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Oncology

# Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017; published online April 21. http://dx.doi.org/10.1016/S1470-2045(17)30279-6.

# WEB APPENDIX

**Participating GOG Institutions:**
The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Oklahoma Health Sciences Center, Seoul National University Hospital, Women's Cancer Center of Nevada, Women and Infants Hospital, University of Colorado Cancer Center – Anschutz Cancer Pavilion, Abramson Cancer Center of the University of Pennsylvania, Duke University Medical Center, MD Anderson Cancer Center, Northwestern University, University of Wisconsin Hospital and Clinics, Gynecologic Oncology of West Michigan PLLC, University of Iowa Hospitals and Clinics, University of New Mexico, Samsung Medical Center, Ohio State University Comprehensive Cancer Center, Wayne State University/Karmanos Cancer Institute, University of Virginia, Saitama Medical University International Medical Center, Abington Memorial Hospital, University of Texas Southwestern Medical Center, Indiana University Hospital/Melvin and Bren Simon Cancer Center, Mount Sinai School of Medicine, Wake Forest University Health Sciences, Fox Chase Cancer Center, University of California Medical Center at Irvine-Orange Campus, Stony Brook University Medical Center, Memorial Sloan Kettering Cancer Center, University of Chicago, Case Western Reserve University, University of Texas – Galveston, Virginia Commonwealth University, Georgia Regents University, Rush University Medical Center, The Hospital of Central Connecticut, Froedtert and the Medical College of Wisconsin, Saint Vincent Hospital, Cooper Hospital University Medical Center, University of Massachusetts Memorial Health Care, Cancer Research Consortium of West Michigan NCORP, Delaware/Christiana Care CCOP, University of Mississippi Medical Center, Aurora Women's Pavilion of Aurora West Allis Medical Center, UCSF-Mount Zion, Carle Cancer Center, University of California at Los Angeles Health System, Penn State Milton S. Hershey Medical Center, State University of New York Downstate Medical Center, Cleveland Clinic Foundation, Washington University School of Medicine, Fletcher Allen Health Care, Carolinas Medical Center/Levine Cancer Institute, Henry Ford Hospital, Hartford Hospital, University of Rochester, Metro-Minnesota CCOP, Northern Indiana Cancer Research Consortium and Wichita CCOP.

**Accrual Report by Site and PI**

| Site | N | Excluded | Principal Investigator |
|---|---|---|---|
| CCOP | 70 | 2 | Anthony Evans, Rakesh Gaur, Radhika Gogoi, Gilbert Padula |
| OKLAHOMA | 67 | 4 | Robert Mannel |
| KOREAGOG | 50 | 5 | Joo-Hyun Nam |
| GOGJAPAN | 31 | 0 | Keichii Fujiwara |
| COLUMBUS | 27 | 2 | David O'Malley |
| IRVINE | 26 | 3 | Krishnansu Tewari |
| COLORADO | 24 | 1 | Susan Davidson |
| WCC-UNEV | 23 | 1 | Nicola Spirtos |
| PENN | 21 | 0 | Stephen Rubin |
| WOM & INF | 21 | 0 | Paul DiSilvestro |
| DUKE | 20 | 0 | Angela Alvarez-Secord |
| NEW MEXICO | 19 | 0 | Carolyn Muller |
| WISCONSIN | 18 | 0 | David Kushner |
| UNC | 17 | 1 | Linda Van Le |
| NORTHWESTN | 15 | 1 | Emily Berry |
| SUNY SB | 15 | 0 | Michael Pearl |
| WESTRNMICH | 15 | 0 | Gordon Downey |
| RPCI | 14 | 0 | Shashikant Lele |
| COOPER | 14 | 2 | David Warshaw |
| ANDERSON | 14 | 0 | Robert Coleman |
| IOWA | 13 | 0 | David Bender |
| CENT CONN | 13 | 0 | Thomas Rutherford |
| RUSH | 11 | 0 | Jacob Rotmensch |
| WAYNE ST | 10 | 1 | Robert Morris |
| VIRGINIA | 10 | 0 | Susan Modesitt |
| FOX CHASE | 9 | 0 | Robert Burger |
| DALLAS | 8 | 2 | David Scott Miller |
| INDIANA | 8 | 0 | Jeanne Schilder |
| W REED | 7 | 0 | Michael Stany |
| MISS | 7 | 0 | Tate Thigpen |
| CASE WEST | 7 | 1 | Steven Waggoner |
| TAMPA | 7 | 0 | Robert Wenham |
| GALVESTON | 6 | 0 | Lyuba Levine |
| ABINGTON | 5 | 0 | Parviz Hanjani |
| HUTCHCRC | 5 | 0 | Heidi Gray |
| HERSHEY | 5 | 1 | James Fanning |
| W FOREST | 5 | 0 | Samuel Lentz |
| CLEV | 5 | 0 | Peter Rose |
| MEMORIAL | 5 | 0 | Oliver Zivanovic |
| CINN | 4 | 1 | Eric Eisenhauser |
| WASH U | 4 | 0 | David Mutch |
| MINN | 3 | 0 | Melissa Geller |
| MASS | 3 | 0 | Susan Zwezig |
| CHICAGO | 3 | 0 | Alfred Guirguis |
| GA CORE | 3 | 1 | Sharad Ghamande |
| AURORA HC | 2 | 0 | Susan Davidson |
| UCSF-ZION | 2 | 0 | John Chan |
| UCLA | 1 | 0 | Robin Farias-Eisner |
| SUNY-DWN | 1 | 0 | Ovadia Abulafia |
| MAYO | 1 | 0 | Jamie Bakkum-Gamez |
| CAROLINAS | 1 | 0 | Robert Higgins |

**Supplemental Table: CTCAE v3.0 toxicity details by category and attribution in the Intention-To-Treat (ITT) population who received therapy.**

| | Carboplatin/Paclitaxel (CP) (n=327) | | | | | CP + Bevacizumab (n=330) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. and (%) of Patients by Grade | | | | | No. and (%) of Patients by Grade | | | | |
| | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| **Organ System/Term** | | | | | | | | | | |
| **Auditory/Ear** | **1** | **22** | **0** | **0** | **0** | **1** | **28** | **3** | **0** | **0** |
| | **(0.3)** | **(6.7)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.3)** | **(8.5)** | **(0.9)** | **(0.0)** | **(0.0)** |
| Otitis Middle Ear | 0 | 1 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) |
| Hearing (Without Monitoring Program) | 0 | 6 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 0 |
| | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (2.7) | (0.3) | (0.0) | (0.0) |
| Hearing (Monitoring Program) | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Tinnitus | 0 | 16 | 0 | 0 | 0 | 0 | 18 | 1 | 0 | 0 |
| | (0.0) | (4.9) | (0.0) | (0.0) | (0.0) | (0.0) | (5.5) | (0.3) | (0.0) | (0.0) |
| Auditory/Ear - Other | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| **Allergy/Immunology** | **37** | **31** | **25** | **1** | **0** | **55** | **45** | **31** | **1** | **0** |
| | **(11.3)** | **(9.5)** | **(7.6)** | **(0.3)** | **(0.0)** | **(16.7)** | **(13.6)** | **(9.4)** | **(0.3)** | **(0.0)** |
| Allergic Reaction/Hypersensitivity | 27 | 29 | 25 | 1 | 0 | 18 | 38 | 31 | 1 | 0 |
| | (8.3) | (8.9) | (7.6) | (0.3) | (0.0) | (5.5) | (11.5) | (9.4) | (0.3) | (0.0) |
| Autoimmune Reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Rhinitis | 11 | 2 | 0 | 0 | 0 | 50 | 10 | 0 | 0 | 0 |
| | (3.4) | (0.6) | (0.0) | (0.0) | (0.0) | (15.2) | (3.0) | (0.0) | (0.0) | (0.0) |
| Vasculitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Allergy/Immunology - Other | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| **Coagulation** | **3** | **0** | **0** | **0** | **0** | **4** | **2** | **6** | **0** | **0** |
| | **(0.9)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(1.2)** | **(0.6)** | **(1.8)** | **(0.0)** | **(0.0)** |
| Inr | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 5 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (1.5) | (0.0) | (0.0) |
| Dic | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Ptt | 2 | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.6) | (0.3) | (0.0) | (0.0) |
| Thrombotic Microangiopathy | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Constitutional Symptoms** | **151** | **115** | **9** | **0** | **0** | **114** | **144** | **29** | **0** | **0** |
| | **(46.2)** | **(35.2)** | **(2.8)** | **(0.0)** | **(0.0)** | **(34.5)** | **(43.6)** | **(8.8)** | **(0.0)** | **(0.0)** |
| Fatigue | 152 | 104 | 8 | 0 | 0 | 130 | 121 | 27 | 0 | 0 |
| | (46.5) | (31.8) | (2.4) | (0.0) | (0.0) | (39.4) | (36.7) | (8.2) | (0.0) | (0.0) |
| Fever | 30 | 1 | 0 | 0 | 0 | 37 | 8 | 0 | 0 | 0 |
| | (9.2) | (0.3) | (0.0) | (0.0) | (0.0) | (11.2) | (2.4) | (0.0) | (0.0) | (0.0) |
| Weight Loss | 9 | 4 | 0 | 0 | 0 | 23 | 28 | 1 | 0 | 0 |
| | (2.8) | (1.2) | (0.0) | (0.0) | (0.0) | (7.0) | (8.5) | (0.3) | (0.0) | (0.0) |
| Sweating | 10 | 2 | 0 | 0 | 0 | 8 | 1 | 0 | 0 | 0 |
| | (3.1) | (0.6) | (0.0) | (0.0) | (0.0) | (2.4) | (0.3) | (0.0) | (0.0) | (0.0) |
| Rigors/Chills | 7 | 1 | 0 | 0 | 0 | 15 | 0 | 0 | 0 | 0 |
| | (2.1) | (0.3) | (0.0) | (0.0) | (0.0) | (4.5) | (0.0) | (0.0) | (0.0) | (0.0) |
| Weight Gain | 12 | 5 | 1 | 0 | 0 | 11 | 15 | 1 | 0 | 0 |
| | (3.7) | (1.5) | (0.3) | (0.0) | (0.0) | (3.3) | (4.5) | (0.3) | (0.0) | (0.0) |
| Insomnia | 41 | 7 | 0 | 0 | 0 | 42 | 16 | 3 | 0 | 0 |
| | (12.5) | (2.1) | (0.0) | (0.0) | (0.0) | (12.7) | (4.8) | (0.9) | (0.0) | (0.0) |
| Constitutional Symptoms - Other | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.6) | (0.0) | (0.0) | (0.0) |
| **Cardiac** | **20** | **8** | **5** | **0** | **0** | **52** | **74** | **41** | **5** | **0** |
| | **(6.1)** | **(2.4)** | **(1.5)** | **(0.0)** | **(0.0)** | **(15.8)** | **(22.4)** | **(12.4)** | **(1.5)** | **(0.0)** |
| Hypertension | 7 | 1 | 2 | 0 | 0 | 34 | 66 | 39 | 0 | 0 |
| | (2.1) | (0.3) | (0.6) | (0.0) | (0.0) | (10.3) | (20.0) | (11.8) | (0.0) | (0.0) |
| Palpitations | 9 | 4 | 0 | 0 | 0 | 14 | 5 | 0 | 0 | 0 |
| | (2.8) | (1.2) | (0.0) | (0.0) | (0.0) | (4.2) | (1.5) | (0.0) | (0.0) | (0.0) |
| Cardiac Ischemia/Infarction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.9) | (0.0) |
| Cardiac Arrhythmia - Other | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) |
| Ventricular Arrhythmia - Pvcs | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ventricular Arrhythmia - Fibrillation | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ventricular Arrhythmia - Tachycardia | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) |
| S/N Arrhythmia: Atrial Fibrillation | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) |
| S/N Arrhythmia: Sinus Bradycardia | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| S/N Arrhythmia: Sinus Tachycardia | 5 | 1 | 0 | 0 | 0 | 13 | 1 | 0 | 0 | 0 |
| | (1.5) | (0.3) | (0.0) | (0.0) | (0.0) | (3.9) | (0.3) | (0.0) | (0.0) | (0.0) |
| Supraventricular Tachycardia | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Prolonged Qtc Interval | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Left Venticular Diastolic Dysfunction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Hypotension | 1 | 1 | 1 | 0 | 0 | 3 | 10 | 0 | 0 | 0 |
| | (0.3) | (0.3) | (0.3) | (0.0) | (0.0) | (0.9) | (3.0) | (0.0) | (0.0) | (0.0) |
| Cardiac Troponin I (Ctni) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) |
| Cardiac General - Other | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Dermatology/Skin** | **38** | **239** | **1** | **0** | **0** | **45** | **241** | **8** | **1** | **0** |
| | **(11.6)** | **(73.1)** | **(0.3)** | **(0.0)** | **(0.0)** | **(13.6)** | **(73.0)** | **(2.4)** | **(0.3)** | **(0.0)** |
| Hair Loss/Alopecia (Scalp Or Body) | 30 | 232 | 0 | 0 | 0 | 30 | 241 | 0 | 0 | 0 |
| | (9.2) | (70.9) | (0.0) | (0.0) | (0.0) | (9.1) | (73.0) | (0.0) | (0.0) | (0.0) |
| Bruising | 10 | 1 | 0 | 0 | 0 | 15 | 0 | 0 | 0 | 0 |
| | (3.1) | (0.3) | (0.0) | (0.0) | (0.0) | (4.5) | (0.0) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Urticaria | 3 | 1 | 1 | 0 | 0 | 10 | 5 | 1 | 0 | 0 |
| | (0.9) | (0.3) | (0.3) | (0.0) | (0.0) | (3.0) | (1.5) | (0.3) | (0.0) | (0.0) |
| Pruritus | 21 | 6 | 0 | 0 | 0 | 29 | 9 | 1 | 0 | 0 |
| | (6.4) | (1.8) | (0.0) | (0.0) | (0.0) | (8.8) | (2.7) | (0.3) | (0.0) | (0.0) |
| Flushing | 7 | 4 | 0 | 0 | 0 | 16 | 4 | 0 | 0 | 0 |
| | (2.1) | (1.2) | (0.0) | (0.0) | (0.0) | (4.8) | (1.2) | (0.0) | (0.0) | (0.0) |
| Dry Skin | 5 | 0 | 0 | 0 | 0 | 16 | 8 | 0 | 0 | 0 |
| | (1.5) | (0.0) | (0.0) | (0.0) | (0.0) | (4.8) | (2.4) | (0.0) | (0.0) | (0.0) |
| Erythema Multiforme | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Hand-Foot | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.6) | (0.0) | (0.0) |
| Injection Site Reaction | 2 | 1 | 0 | 0 | 0 | 5 | 3 | 0 | 0 | 0 |
| | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) | (1.5) | (0.9) | (0.0) | (0.0) | (0.0) |
| Hyperpigmentation | 1 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (2.4) | (0.0) | (0.0) | (0.0) | (0.0) |
| Rash | 35 | 17 | 0 | 0 | 0 | 59 | 20 | 1 | 0 | 0 |
| | (10.7) | (5.2) | (0.0) | (0.0) | (0.0) | (17.9) | (6.1) | (0.3) | (0.0) | (0.0) |
| Nail Changes | 6 | 2 | 0 | 0 | 0 | 25 | 8 | 0 | 0 | 0 |
| | (1.8) | (0.6) | (0.0) | (0.0) | (0.0) | (7.6) | (2.4) | (0.0) | (0.0) | (0.0) |
| Wound Complication, Non-Infectious | 2 | 0 | 0 | 0 | 0 | 5 | 1 | 2 | 1 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.3) | (0.6) | (0.3) | (0.0) |
| Burn | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Cheilitis | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) |
| Acne | 2 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (2.7) | (0.3) | (0.0) | (0.0) | (0.0) |
| Decubitus | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Telangiectasia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ulceration | 0 | 1 | 0 | 0 | 0 | 0 | 8 | 1 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (2.4) | (0.3) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dermatology/Skin - Other | 8 | 2 | 0 | 0 | 0 | 14 | 6 | 1 | 0 | 0 |
| | (2.4) | (0.6) | (0.0) | (0.0) | (0.0) | (4.2) | (1.8) | (0.3) | (0.0) | (0.0) |
| **Death** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **5** |
| | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(1.5)** |
| Death No Ctcae Term - Death Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) |
| Death No Ctcae Term - Disease Progression Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) |
| Death No Ctcae Term - Sudden Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) |
| **Endocrine** | **27** | **6** | **0** | **0** | **0** | **30** | **17** | **1** | **0** | **0** |
| | **(8.3)** | **(1.8)** | **(0.0)** | **(0.0)** | **(0.0)** | **(9.1)** | **(5.2)** | **(0.3)** | **(0.0)** | **(0.0)** |
| Hot Flashes | 26 | 6 | 0 | 0 | 0 | 29 | 11 | 0 | 0 | 0 |
| | (8.0) | (1.8) | (0.0) | (0.0) | (0.0) | (8.8) | (3.3) | (0.0) | (0.0) | (0.0) |
| Hypothyroidism | 1 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Adh Secrection Abnormality | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Hyperthyroidism | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Endocrine - Other | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Gastrointestinal** | **173** | **94** | **18** | **1** | **0** | **132** | **127** | **36** | **2** | **0** |
| | **(52.9)** | **(28.7)** | **(5.5)** | **(0.3)** | **(0.0)** | **(40.0)** | **(38.5)** | **(10.9)** | **(0.6)** | **(0.0)** |
| Nausea | 156 | 36 | 6 | 0 | 0 | 131 | 65 | 12 | 0 | 0 |
| | (47.7) | (11.0) | (1.8) | (0.0) | (0.0) | (39.7) | (19.7) | (3.6) | (0.0) | (0.0) |
| Vomiting | 55 | 20 | 7 | 0 | 0 | 64 | 42 | 5 | 0 | 0 |
| | (16.8) | (6.1) | (2.1) | (0.0) | (0.0) | (19.4) | (12.7) | (1.5) | (0.0) | (0.0) |
| Diarrhea | 88 | 17 | 2 | 0 | 0 | 103 | 27 | 8 | 0 | 0 |
| | (26.9) | (5.2) | (0.6) | (0.0) | (0.0) | (31.2) | (8.2) | (2.4) | (0.0) | (0.0) |
| Constipation | 140 | 40 | 2 | 1 | 0 | 127 | 45 | 4 | 0 | 0 |
| | (42.8) | (12.2) | (0.6) | (0.3) | (0.0) | (38.5) | (13.6) | (1.2) | (0.0) | (0.0) |
| Dehydration | 0 | 9 | 4 | 0 | 0 | 1 | 13 | 7 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (2.8) | (1.2) | (0.0) | (0.0) | (0.3) | (3.9) | (2.1) | (0.0) | (0.0) |
| Anorexia | 70 | 17 | 0 | 0 | 0 | 84 | 30 | 5 | 0 | 0 |
| | (21.4) | (5.2) | (0.0) | (0.0) | (0.0) | (25.5) | (9.1) | (1.5) | (0.0) | (0.0) |
| Mucositis (Clinical Exam) - Larynx | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Mucositis (Clinical Exam) - Oral Cavity | 21 | 2 | 0 | 0 | 0 | 45 | 17 | 0 | 0 | 0 |
| | (6.4) | (0.6) | (0.0) | (0.0) | (0.0) | (13.6) | (5.2) | (0.0) | (0.0) | (0.0) |
| Mucositis (Clinical Exam) - Pharynx | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Mucositis (Functional/Sympt) - Esophagus | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Mucositis (Functional/Sympt) - Oral Cavity | 27 | 7 | 0 | 0 | 0 | 50 | 17 | 1 | 0 | 0 |
| | (8.3) | (2.1) | (0.0) | (0.0) | (0.0) | (15.2) | (5.2) | (0.3) | (0.0) | (0.0) |
| Mucositis (Functional/Sympt) - Rectum | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Mucositis (Functional/Sympt) - Stomach | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Mucositis (Functional/Sympt) - Trachea | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Dry Mouth | 6 | 0 | 0 | 0 | 0 | 14 | 1 | 0 | 0 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (4.2) | (0.3) | (0.0) | (0.0) | (0.0) |
| Ileus | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Dysphagia | 6 | 0 | 0 | 0 | 0 | 13 | 4 | 1 | 0 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (3.9) | (1.2) | (0.3) | (0.0) | (0.0) |
| Esophagitis | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.6) | (0.0) | (0.0) |
| Taste Alteration | 34 | 4 | 0 | 0 | 0 | 40 | 2 | 0 | 0 | 0 |
| | (10.4) | (1.2) | (0.0) | (0.0) | (0.0) | (12.1) | (0.6) | (0.0) | (0.0) | (0.0) |
| Proctitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ascites | 0 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) |
| Colitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.3) | (0.3) | (0.0) |
| Heartburn | 28 | 3 | 0 | 0 | 0 | 36 | 11 | 2 | 0 | 0 |
| | (8.6) | (0.9) | (0.0) | (0.0) | (0.0) | (10.9) | (3.3) | (0.6) | (0.0) | (0.0) |
| Flatulence | 3 | 2 | 0 | 0 | 0 | 8 | 2 | 0 | 0 | 0 |
| | (0.9) | (0.6) | (0.0) | (0.0) | (0.0) | (2.4) | (0.6) | (0.0) | (0.0) | (0.0) |
| Gastritis | 2 | 2 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 |
| | (0.6) | (0.6) | (0.0) | (0.0) | (0.0) | (0.9) | (0.6) | (0.0) | (0.0) | (0.0) |
| Salivary Gland Changes | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ulcer,gi - Esophagus | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Ulcer,gi - Stomach | 1 | 0 | 0 | 0 | 0 | 3 | 2 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.6) | (0.3) | (0.0) | (0.0) |
| Fistula, Gi - Colon/Cecum/Appendix | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) |
| Fistula, Gi - Small Bowel Nos | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Dental: Periodontal | 0 | 0 | 0 | 0 | 0 | 6 | 3 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.9) | (0.0) | (0.0) | (0.0) |
| Dental: Teeth | 0 | 0 | 0 | 0 | 0 | 3 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (1.2) | (0.0) | (0.0) | (0.0) |
| Distention | 19 | 2 | 0 | 0 | 0 | 17 | 10 | 1 | 0 | 0 |
| | (5.8) | (0.6) | (0.0) | (0.0) | (0.0) | (5.2) | (3.0) | (0.3) | (0.0) | (0.0) |
| Hemorrhoids | 1 | 0 | 0 | 0 | 0 | 16 | 3 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (4.8) | (0.9) | (0.0) | (0.0) | (0.0) |
| Incontinence, Anal | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Leak, Gi - Rectum | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Obstruction, Gi - Colon | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Obstruction, Gi - Ileum | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Obstruction, Gi - Small Bowel Nos | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 9 | 0 | 0 |
| | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.3) | (2.7) | (0.0) | (0.0) |
| Perforation, Gi - Colon | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Perforation, Gi - Small Bowel Nos | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.3) | (0.0) | (0.0) |
| Stricture, Gi - Stomach | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Gastrointestinal - Other | 3 | 0 | 0 | 0 | 0 | 7 | 2 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.6) | (0.0) | (0.0) | (0.0) |
| **Renal/Genitourinary** | **31** | **8** | **3** | **0** | **0** | **45** | **13** | **5** | **0** | **0** |
| | **(9.5)** | **(2.4)** | **(0.9)** | **(0.0)** | **(0.0)** | **(13.6)** | **(3.9)** | **(1.5)** | **(0.0)** | **(0.0)** |
| Urinary Frequency | 18 | 9 | 0 | 0 | 0 | 28 | 4 | 0 | 0 | 0 |
| | (5.5) | (2.8) | (0.0) | (0.0) | (0.0) | (8.5) | (1.2) | (0.0) | (0.0) | (0.0) |
| Renal Failure | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) |
| Bladder Spasm | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Incontinence, Urinary | 14 | 1 | 0 | 0 | 0 | 18 | 2 | 0 | 0 | 0 |
| | (4.3) | (0.3) | (0.0) | (0.0) | (0.0) | (5.5) | (0.6) | (0.0) | (0.0) | (0.0) |
| Obstruction, Gu - Ureter | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Obstruction, Gu - Urethra | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Urinary Retention | 2 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) |
| Urinary Color Change | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Cystitis | 0 | 0 | 0 | 0 | 0 | 1 | 4 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (1.2) | (0.3) | (0.0) | (0.0) |
| Renal/Genitourinary - Other | 2 | 0 | 0 | 0 | 0 | 5 | 3 | 2 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.9) | (0.6) | (0.0) | (0.0) |
| **Hemorrhage/Bleeding** | **23** | **1** | **3** | **0** | **0** | **121** | **13** | **5** | **1** | **0** |
| | **(7.0)** | **(0.3)** | **(0.9)** | **(0.0)** | **(0.0)** | **(36.7)** | **(3.9)** | **(1.5)** | **(0.3)** | **(0.0)** |
| Petechiae | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Cns | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) |
| Hematoma | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Anus | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Colon | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.3) | (0.0) | (0.0) |
| Hemorrhage, Gi - Lower Gi Nos | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Oral Cavity | 2 | 0 | 0 | 0 | 0 | 17 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (5.2) | (0.3) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Rectum | 6 | 0 | 0 | 0 | 0 | 18 | 2 | 1 | 0 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (5.5) | (0.6) | (0.3) | (0.0) | (0.0) |
| Hemorrhage, Gi - Stoma | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Stomach | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Hemorrhage, Gi - Upper Gi Nos | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gi - Varices (Rectal) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gu - Bladder | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gu - Ureter | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gu - Urethra | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gu - Urinary Nos | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage, Gu - Vagina | 8 | 0 | 1 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| | (2.4) | (0.0) | (0.3) | (0.0) | (0.0) | (2.7) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage/Pulmonary - Lung | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage/Pulmonary - Nose | 8 | 0 | 0 | 0 | 0 | 99 | 9 | 3 | 0 | 0 |
| | (2.4) | (0.0) | (0.0) | (0.0) | (0.0) | (30.0) | (2.7) | (0.9) | (0.0) | (0.0) |
| Hemorrhage/Pulmonary - Respiratory Tract Nos | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hemorrhage/Bleeding - Other | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Blood/Bone Marrow** | **15** | **48** | **88** | **170** | **1** | **4** | **37** | **76** | **208** | **1** |
| | **(4.6)** | **(14.7)** | **(26.9)** | **(52.0)** | **(0.3)** | **(1.2)** | **(11.2)** | **(23.0)** | **(63.0)** | **(0.3)** |
| Leukocytes | 39 | 124 | 130 | 5 | 0 | 40 | 125 | 127 | 13 | 0 |
| | (11.9) | (37.9) | (39.8) | (1.5) | (0.0) | (12.1) | (37.9) | (38.5) | (3.9) | (0.0) |
| Hemoglobin | 134 | 147 | 18 | 3 | 0 | 155 | 111 | 21 | 1 | 0 |
| | (41.0) | (45.0) | (5.5) | (0.9) | (0.0) | (47.0) | (33.6) | (6.4) | (0.3) | (0.0) |
| Platelets | 126 | 44 | 17 | 2 | 0 | 150 | 57 | 32 | 2 | 0 |
| | (38.5) | (13.5) | (5.2) | (0.6) | (0.0) | (45.5) | (17.3) | (9.7) | (0.6) | (0.0) |
| Neutrophils | 8 | 41 | 86 | 169 | 0 | 2 | 39 | 70 | 206 | 0 |
| | (2.4) | (12.5) | (26.3) | (51.7) | (0.0) | (0.6) | (11.8) | (21.2) | (62.4) | (0.0) |
| Lymphopenia | 4 | 13 | 5 | 0 | 0 | 9 | 13 | 7 | 0 | 0 |
| | (1.2) | (4.0) | (1.5) | (0.0) | (0.0) | (2.7) | (3.9) | (2.1) | (0.0) | (0.0) |
| Myelodysplasia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) |
| Blood/Bone Marrow - Other | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) |
| **Hepatobiliary/Pancreas** | **0** | **0** | **0** | **0** | **0** | **1** | **0** | **0** | **0** | **0** |
| | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.3)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** |
| Cholecystitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Infection** | **2** | **68** | **19** | **0** | **0** | **0** | **83** | **37** | **4** | **2** |
| | **(0.6)** | **(20.8)** | **(5.8)** | **(0.0)** | **(0.0)** | **(0.0)** | **(25.2)** | **(11.2)** | **(1.2)** | **(0.6)** |
| Febrile Neutropenia | 0 | 0 | 9 | 0 | 0 | 0 | 0 | 18 | 1 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (0.0) | (2.8) | (0.0) | (0.0) | (0.0) | (0.0) | (5.5) | (0.3) | (0.3) |
| Inf W/Nml Or Gr 1 Or 2 Anc: External Ear | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Otitis Media Nos | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Lip/Perioral | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Skin(Cellulitis) | 0 | 5 | 1 | 0 | 0 | 0 | 5 | 1 | 0 | 0 |
| | (0.0) | (1.5) | (0.3) | (0.0) | (0.0) | (0.0) | (1.5) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Ungual (Nails) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Anal/Perianal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Colon | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Dental-Tooth | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Oral Cavity-Gums | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Stomach | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Catheter-Related | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Foreign Body | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Wound | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Inf W/Nml Or Gr 1 Or 2 Anc: Blood | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Bladder | 0 | 3 | 0 | 0 | 0 | 0 | 7 | 1 | 0 | 0 |
| | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Kidney | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Urinary Tract Nos | 0 | 21 | 2 | 0 | 0 | 0 | 23 | 3 | 1 | 0 |
| | (0.0) | (6.4) | (0.6) | (0.0) | (0.0) | (0.0) | (7.0) | (0.9) | (0.3) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Joint | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Soft Tissue Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Brain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Meninges | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Conjunctiva | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Eye Nos | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Bronchus | 0 | 4 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| | (0.0) | (1.2) | (0.3) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Lung(Pneumonia) | 0 | 4 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 |
| | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.6) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Nose | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Inf W/Nml Or Gr 1 Or 2 Anc: Pharynx | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Sinus | 0 | 5 | 0 | 0 | 0 | 0 | 17 | 1 | 0 | 0 |
| | (0.0) | (1.5) | (0.0) | (0.0) | (0.0) | (0.0) | (5.2) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Upper Airway Nos | 0 | 11 | 0 | 0 | 0 | 0 | 20 | 0 | 0 | 0 |
| | (0.0) | (3.4) | (0.0) | (0.0) | (0.0) | (0.0) | (6.1) | (0.0) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Pelvis Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Vagina | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (2.7) | (0.3) | (0.0) | (0.0) |
| Inf W/Nml Or Gr 1 Or 2 Anc: Vulva | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Skin (Cellulitis) | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Oral Cavity-Gums | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Catheter-Related | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Foreign Body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Blood | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) |
| Inf W/Gr 3 Or 4 Anc: Bladder (Urinary) | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Urinary Tract Nos | 0 | 5 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (1.5) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Joint | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Inf W/Gr 3 Or 4 Anc: Eye Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Bronchus | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Lung (Pneumonia) | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Nose | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Pharynx | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Sinus | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Upper Airway Nos | 0 | 4 | 1 | 0 | 0 | 0 | 7 | 0 | 0 | 0 |
| | (0.0) | (1.2) | (0.3) | (0.0) | (0.0) | (0.0) | (2.1) | (0.0) | (0.0) | (0.0) |
| Inf W/Gr 3 Or 4 Anc: Vagina | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Middle Ear | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Skin (Cellulitis) | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Abdomen Nos | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Dental-Tooth | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Oral Cavity-Gums | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Catheter-Related | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Inf Unknown Anc: Foreign Body | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Inf Unknown Anc: Bladder (Urinary) | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Urinary Tract Nos | 0 | 6 | 0 | 0 | 0 | 0 | 6 | 2 | 0 | 0 |
| | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.6) | (0.0) | (0.0) |
| Inf Unknown Anc: Soft Tissue Nos | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Inf Unknown Anc: Eye Nos | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Bronchus | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Nose | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Pharynx | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Sinus | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Inf Unknown Anc: Upper Airway Nos | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.0) | (0.0) | (0.0) |
| Colitis, Infectious (Eg.C. Difficile) | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) |
| Opportunisitic Inf Assoc. W/Gr 2 Lymphopenia | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Infection - Other | 3 | 4 | 1 | 0 | 0 | 3 | 5 | 0 | 1 | 0 |
| | (0.9) | (1.2) | (0.3) | (0.0) | (0.0) | (0.9) | (1.5) | (0.0) | (0.3) | (0.0) |
| **Lymphatics** | **40** | **2** | **0** | **0** | **0** | **36** | **8** | **0** | **0** | **0** |
| | **(12.2)** | **(0.6)** | **(0.0)** | **(0.0)** | **(0.0)** | **(10.9)** | **(2.4)** | **(0.0)** | **(0.0)** | **(0.0)** |
| Edema: Head and Neck | 1 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) |
| Edema: Limb | 39 | 2 | 0 | 0 | 0 | 31 | 8 | 0 | 0 | 0 |
| | (11.9) | (0.6) | (0.0) | (0.0) | (0.0) | (9.4) | (2.4) | (0.0) | (0.0) | (0.0) |
| Edema: Trunk/Genital | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) |
| Lymphedema-Related Fibrosis | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Lymphatics - Other | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Secondary Malignancy** | **0** | **0** | **0** | **0** | **1** | **0** | **0** | **0** | **0** | **1** |
| | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.3)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.0)** | **(0.3)** |
| 2nd Mal: Poss. Related to Cancer Rx (Specify) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) |
| **Musculoskeletal/Soft Tissue** | **22** | **12** | **1** | **0** | **0** | **48** | **22** | **6** | **0** | **0** |
| | **(6.7)** | **(3.7)** | **(0.3)** | **(0.0)** | **(0.0)** | **(14.5)** | **(6.7)** | **(1.8)** | **(0.0)** | **(0.0)** |
| Muscle Weakness - Extremity-Lower | 5 | 7 | 0 | 0 | 0 | 9 | 5 | 0 | 0 | 0 |
| | (1.5) | (2.1) | (0.0) | (0.0) | (0.0) | (2.7) | (1.5) | (0.0) | (0.0) | (0.0) |
| Muscle Weakness - Extremity-Upper | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.3) | (0.0) | (0.0) |
| Muscle Weakness - Left-Sided | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Muscle Weakness - Right-Sided | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Muscle Weakness - Whole Body/Generalized | 13 | 4 | 1 | 0 | 0 | 21 | 7 | 2 | 0 | 0 |
| | (4.0) | (1.2) | (0.3) | (0.0) | (0.0) | (6.4) | (2.1) | (0.6) | (0.0) | (0.0) |
| Arthritis | 3 | 1 | 0 | 0 | 0 | 13 | 2 | 1 | 0 | 0 |
| | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) | (3.9) | (0.6) | (0.3) | (0.0) | (0.0) |
| Cervical Spine Rom | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Gait/Walking | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Extremity-Upper (Function) | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Fracture | 0 | 2 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Joint Effusion | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Joint-Function | 2 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) |
| Osteoporosis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Soft Tissue Necrosis - Abdomen | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Musculoskeletal/St: Other | 1 | 0 | 0 | 0 | 0 | 6 | 5 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (1.5) | (0.0) | (0.0) | (0.0) |
| **Metabolic/Laboratory** | **63** | **39** | **29** | **3** | **0** | **85** | **58** | **60** | **7** | **0** |
| | **(19.3)** | **(11.9)** | **(8.9)** | **(0.9)** | **(0.0)** | **(25.8)** | **(17.6)** | **(18.2)** | **(2.1)** | **(0.0)** |
| Hypomagnesemia | 47 | 10 | 0 | 0 | 0 | 77 | 15 | 1 | 0 | 0 |
| | (14.4) | (3.1) | (0.0) | (0.0) | (0.0) | (23.3) | (4.5) | (0.3) | (0.0) | (0.0) |
| Hypercalcemia | 6 | 0 | 0 | 0 | 0 | 14 | 1 | 0 | 1 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (4.2) | (0.3) | (0.0) | (0.3) | (0.0) |
| Hypoglycemia | 7 | 1 | 0 | 0 | 0 | 16 | 4 | 0 | 0 | 0 |
| | (2.1) | (0.3) | (0.0) | (0.0) | (0.0) | (4.8) | (1.2) | (0.0) | (0.0) | (0.0) |
| Hypokalemia | 29 | 0 | 6 | 1 | 0 | 40 | 0 | 4 | 1 | 0 |
| | (8.9) | (0.0) | (1.8) | (0.3) | (0.0) | (12.1) | (0.0) | (1.2) | (0.3) | (0.0) |
| Hyperglycemia | 38 | 25 | 16 | 1 | 0 | 53 | 34 | 13 | 1 | 0 |
| | (11.6) | (7.6) | (4.9) | (0.3) | (0.0) | (16.1) | (10.3) | (3.9) | (0.3) | (0.0) |
| Hyperkalemia | 9 | 1 | 0 | 0 | 0 | 23 | 1 | 5 | 0 | 0 |
| | (2.8) | (0.3) | (0.0) | (0.0) | (0.0) | (7.0) | (0.3) | (1.5) | (0.0) | (0.0) |
| Hypermagnesemia | 1 | 0 | 1 | 0 | 0 | 12 | 0 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.3) | (0.0) | (0.0) | (3.6) | (0.0) | (0.3) | (0.0) | (0.0) |
| Hypocalcemia | 9 | 7 | 1 | 0 | 0 | 28 | 12 | 1 | 0 | 0 |
| | (2.8) | (2.1) | (0.3) | (0.0) | (0.0) | (8.5) | (3.6) | (0.3) | (0.0) | (0.0) |
| Hypernatremia | 6 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.0) | (0.0) | (0.0) | (0.0) |
| Amylase | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Bicarbonate, Serum-Low | 3 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) |
| Cpk | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Cholesterol,serum High | 2 | 0 | 0 | 0 | 0 | 9 | 4 | 0 | 1 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (2.7) | (1.2) | (0.0) | (0.3) | (0.0) |
| Hypertriglyceridemia | 2 | 0 | 1 | 0 | 0 | 4 | 5 | 2 | 0 | 0 |
| | (0.6) | (0.0) | (0.3) | (0.0) | (0.0) | (1.2) | (1.5) | (0.6) | (0.0) | (0.0) |
| Hyperuricemia | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) |
| Hyponatremia | 16 | 0 | 3 | 0 | 0 | 44 | 0 | 11 | 1 | 0 |
| | (4.9) | (0.0) | (0.9) | (0.0) | (0.0) | (13.3) | (0.0) | (3.3) | (0.3) | (0.0) |
| Hypophosphatemia | 7 | 6 | 3 | 0 | 0 | 8 | 9 | 4 | 0 | 0 |
| | (2.1) | (1.8) | (0.9) | (0.0) | (0.0) | (2.4) | (2.7) | (1.2) | (0.0) | (0.0) |
| Lipase | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Bilirubin | 3 | 0 | 1 | 0 | 0 | 10 | 1 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.3) | (0.0) | (0.0) | (3.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Alkaline Phosphatase | 23 | 1 | 0 | 0 | 0 | 29 | 2 | 1 | 0 | 0 |
| | (7.0) | (0.3) | (0.0) | (0.0) | (0.0) | (8.8) | (0.6) | (0.3) | (0.0) | (0.0) |
| Ast | 24 | 7 | 0 | 1 | 0 | 41 | 8 | 2 | 1 | 0 |
| | (7.3) | (2.1) | (0.0) | (0.3) | (0.0) | (12.4) | (2.4) | (0.6) | (0.3) | (0.0) |
| Alt | 23 | 3 | 1 | 1 | 0 | 25 | 6 | 4 | 2 | 0 |
| | (7.0) | (0.9) | (0.3) | (0.3) | (0.0) | (7.6) | (1.8) | (1.2) | (0.6) | (0.0) |
| Ggt | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) |
| Hypoalbuminemia | 14 | 7 | 0 | 0 | 0 | 24 | 10 | 2 | 0 | 0 |
| | (4.3) | (2.1) | (0.0) | (0.0) | (0.0) | (7.3) | (3.0) | (0.6) | (0.0) | (0.0) |
| Gfr | 2 | 0 | 0 | 0 | 0 | 5 | 2 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.5) | (0.6) | (0.0) | (0.0) | (0.0) |
| Creatinine | 14 | 4 | 0 | 0 | 0 | 35 | 10 | 2 | 0 | 0 |
| | (4.3) | (1.2) | (0.0) | (0.0) | (0.0) | (10.6) | (3.0) | (0.6) | (0.0) | (0.0) |
| Proteinuria | 3 | 0 | 0 | 0 | 0 | 20 | 16 | 27 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (6.1) | (4.8) | (8.2) | (0.0) | (0.0) |
| Metabolic/Laboratory - Other | 8 | 1 | 1 | 0 | 0 | 11 | 2 | 1 | 0 | 0 |
| | (2.4) | (0.3) | (0.3) | (0.0) | (0.0) | (3.3) | (0.6) | (0.3) | (0.0) | (0.0) |
| **Neurology** | **185** | **70** | **15** | **2** | **0** | **154** | **81** | **25** | **4** | **0** |
| | **(56.6)** | **(21.4)** | **(4.6)** | **(0.6)** | **(0.0)** | **(46.7)** | **(24.5)** | **(7.6)** | **(1.2)** | **(0.0)** |
| Neuropathy-Motor | 11 | 6 | 0 | 1 | 0 | 5 | 5 | 1 | 0 | 0 |
| | (3.4) | (1.8) | (0.0) | (0.3) | (0.0) | (1.5) | (1.5) | (0.3) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Neuropathy-Sensory | 190 | 49 | 12 | 0 | 0 | 173 | 60 | 5 | 1 | 0 |
| | (58.1) | (15.0) | (3.7) | (0.0) | (0.0) | (52.4) | (18.2) | (1.5) | (0.3) | (0.0) |
| Neuropathy,cranial - Cn I Smell | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Neuropathy,cranial - Cn Iii Pupil | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Neuropathy,cranial - Cn Vii Motor-Face | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Neuropathy,cranial - Cn Viii Hearing/Balance | 1 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Dizziness | 24 | 3 | 0 | 0 | 0 | 39 | 5 | 3 | 0 | 0 |
| | (7.3) | (0.9) | (0.0) | (0.0) | (0.0) | (11.8) | (1.5) | (0.9) | (0.0) | (0.0) |
| Syncope | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 9 | 0 | 0 |
| | (0.0) | (0.0) | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (2.7) | (0.0) | (0.0) |
| Memory Impairment | 7 | 0 | 0 | 0 | 0 | 10 | 3 | 0 | 0 | 0 |
| | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) | (3.0) | (0.9) | (0.0) | (0.0) | (0.0) |
| Confusion | 1 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.6) | (0.0) | (0.0) |
| Ataxia | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Cns Ischemia | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 4 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.3) | (1.2) | (0.0) | (0.0) |
| Cognitive Disturbance | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) |
| Involuntary Movement | 3 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Irritability | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Seizure | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Speech Impairment | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.3) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tremor | 4 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) |
| Mood Alteration - Agitation | 3 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Mood Alteration - Anxiety | 32 | 9 | 0 | 0 | 0 | 35 | 17 | 1 | 0 | 0 |
| | (9.8) | (2.8) | (0.0) | (0.0) | (0.0) | (10.6) | (5.2) | (0.3) | (0.0) | (0.0) |
| Mood Alteration - Depression | 36 | 11 | 0 | 0 | 0 | 23 | 22 | 3 | 2 | 0 |
| | (11.0) | (3.4) | (0.0) | (0.0) | (0.0) | (7.0) | (6.7) | (0.9) | (0.6) | (0.0) |
| Encephalopathy | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Mental Status | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Neurology - Other | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.3) | (0.0) |
| **Ocular/Visual** | **39** | **9** | **1** | **0** | **0** | **58** | **14** | **3** | **0** | **0** |
| | **(11.9)** | **(2.8)** | **(0.3)** | **(0.0)** | **(0.0)** | **(17.6)** | **(4.2)** | **(0.9)** | **(0.0)** | **(0.0)** |
| Blurred Vision | 29 | 8 | 1 | 0 | 0 | 39 | 10 | 2 | 0 | 0 |
| | (8.9) | (2.4) | (0.3) | (0.0) | (0.0) | (11.8) | (3.0) | (0.6) | (0.0) | (0.0) |
| Diplopia | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Flashing Lights/Floaters | 5 | 1 | 0 | 0 | 0 | 17 | 1 | 0 | 0 | 0 |
| | (1.5) | (0.3) | (0.0) | (0.0) | (0.0) | (5.2) | (0.3) | (0.0) | (0.0) | (0.0) |
| Photophobia | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Cataract | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.3) | (0.0) | (0.0) |
| Dry Eye | 2 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) |
| Watery Eye | 7 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) |
| Eyelid Dysfunction | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Scleral Necrosis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Ocular/Visual - Other | 7 | 0 | 0 | 0 | 0 | 8 | 1 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (2.1) | (0.0) | (0.0) | (0.0) | (0.0) | (2.4) | (0.3) | (0.0) | (0.0) | (0.0) |
| **Pulmonary/Upper Respiratory** | **103** | **21** | **6** | **0** | **0** | **135** | **38** | **13** | **1** | **0** |
| | **(31.5)** | **(6.4)** | **(1.8)** | **(0.0)** | **(0.0)** | **(40.9)** | **(11.5)** | **(3.9)** | **(0.3)** | **(0.0)** |
| Dyspnea | 60 | 18 | 4 | 0 | 0 | 70 | 25 | 9 | 1 | 0 |
| | (18.3) | (5.5) | (1.2) | (0.0) | (0.0) | (21.2) | (7.6) | (2.7) | (0.3) | (0.0) |
| Pleural Effusion | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pneumonitis | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Cough | 56 | 0 | 2 | 0 | 0 | 86 | 12 | 3 | 0 | 0 |
| | (17.1) | (0.0) | (0.6) | (0.0) | (0.0) | (26.1) | (3.6) | (0.9) | (0.0) | (0.0) |
| Voice Changes | 6 | 0 | 0 | 0 | 0 | 44 | 3 | 1 | 0 | 0 |
| | (1.8) | (0.0) | (0.0) | (0.0) | (0.0) | (13.3) | (0.9) | (0.3) | (0.0) | (0.0) |
| Aspiration | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) |
| Bronchospasm | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Edema, Larynx | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Nasal/Paranasal Reactions | 9 | 0 | 0 | 0 | 0 | 45 | 3 | 0 | 0 | 0 |
| | (2.8) | (0.0) | (0.0) | (0.0) | (0.0) | (13.6) | (0.9) | (0.0) | (0.0) | (0.0) |
| Airway Obstruction - Bronchus | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Airway Obstruction - Larynx | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pulmonary: Other | 2 | 1 | 0 | 0 | 0 | 8 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) | (2.4) | (0.3) | (0.0) | (0.0) | (0.0) |
| **Pain** | **131** | **94** | **16** | **0** | **0** | **107** | **115** | **48** | **2** | **0** |
| | **(40.1)** | **(28.7)** | **(4.9)** | **(0.0)** | **(0.0)** | **(32.4)** | **(34.8)** | **(14.5)** | **(0.6)** | **(0.0)** |
| Pain: External Ear | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Middle Ear | 4 | 2 | 0 | 0 | 0 | 5 | 3 | 0 | 0 | 0 |
| | (1.2) | (0.6) | (0.0) | (0.0) | (0.0) | (1.5) | (0.9) | (0.0) | (0.0) | (0.0) |
| Pain: Cardiac/ Heart | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain: Lip | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Skin | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Face | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Oral - Gums | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Scalp | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.6) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Abdominal Pain Nos | 72 | 22 | 3 | 0 | 0 | 74 | 28 | 19 | 1 | 0 |
| | (22.0) | (6.7) | (0.9) | (0.0) | (0.0) | (22.4) | (8.5) | (5.8) | (0.3) | (0.0) |
| Pain: Anus | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Dental/Teeth/Peridontal | 0 | 0 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.8) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Esophagus | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Oral Cavity | 3 | 0 | 0 | 0 | 0 | 11 | 3 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (3.3) | (0.9) | (0.0) | (0.0) | (0.0) |
| Pain: Rectum | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.3) | (0.0) | (0.0) |
| Pain: Stomach | 4 | 0 | 0 | 0 | 0 | 7 | 0 | 1 | 0 | 0 |
| | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (0.0) | (0.3) | (0.0) | (0.0) |
| Pain: Pain Nos | 2 | 2 | 0 | 0 | 0 | 6 | 0 | 2 | 0 | 0 |
| | (0.6) | (0.6) | (0.0) | (0.0) | (0.0) | (1.8) | (0.0) | (0.6) | (0.0) | (0.0) |
| Pain: Tumor | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Bladder | 3 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Kidney | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Bone | 13 | 8 | 1 | 0 | 0 | 19 | 7 | 5 | 0 | 0 |
| | (4.0) | (2.4) | (0.3) | (0.0) | (0.0) | (5.8) | (2.1) | (1.5) | (0.0) | (0.0) |
| Pain: Joint | 66 | 31 | 4 | 0 | 0 | 86 | 62 | 8 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (20.2) | (9.5) | (1.2) | (0.0) | (0.0) | (26.1) | (18.8) | (2.4) | (0.0) | (0.0) |
| Pain: Muscle | 38 | 18 | 3 | 0 | 0 | 63 | 32 | 4 | 1 | 0 |
| | (11.6) | (5.5) | (0.9) | (0.0) | (0.0) | (19.1) | (9.7) | (1.2) | (0.3) | (0.0) |
| Pain: Back | 22 | 13 | 1 | 0 | 0 | 46 | 15 | 2 | 0 | 0 |
| | (6.7) | (4.0) | (0.3) | (0.0) | (0.0) | (13.9) | (4.5) | (0.6) | (0.0) | (0.0) |
| Pain: Buttock | 1 | 0 | 0 | 0 | 0 | 4 | 1 | 1 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.3) | (0.3) | (0.0) | (0.0) |
| Pain: Extremity-Limb | 25 | 21 | 0 | 0 | 0 | 56 | 24 | 11 | 0 | 0 |
| | (7.6) | (6.4) | (0.0) | (0.0) | (0.0) | (17.0) | (7.3) | (3.3) | (0.0) | (0.0) |
| Pain: Neck | 0 | 1 | 0 | 0 | 0 | 23 | 9 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (7.0) | (2.7) | (0.0) | (0.0) | (0.0) |
| Pain: Head/Headache | 49 | 13 | 3 | 0 | 0 | 81 | 35 | 13 | 0 | 0 |
| | (15.0) | (4.0) | (0.9) | (0.0) | (0.0) | (24.5) | (10.6) | (3.9) | (0.0) | (0.0) |
| Pain: Neuralgia | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Eye | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.6) | (0.0) | (0.0) | (0.0) |
| Pain: Larynx | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Pleura | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Sinus | 0 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Throat/Pharynx/Larynx | 9 | 1 | 0 | 0 | 0 | 21 | 6 | 0 | 0 | 0 |
| | (2.8) | (0.3) | (0.0) | (0.0) | (0.0) | (6.4) | (1.8) | (0.0) | (0.0) | (0.0) |
| Pain: Chest Wall | 7 | 3 | 1 | 0 | 0 | 10 | 1 | 2 | 0 | 0 |
| | (2.1) | (0.9) | (0.3) | (0.0) | (0.0) | (3.0) | (0.3) | (0.6) | (0.0) | (0.0) |
| Pain: Chest /Thorax Nos | 5 | 2 | 0 | 0 | 0 | 19 | 5 | 3 | 0 | 0 |
| | (1.5) | (0.6) | (0.0) | (0.0) | (0.0) | (5.8) | (1.5) | (0.9) | (0.0) | (0.0) |
| Pain: Breast | 3 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.9) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Pain: Pelvis | 7 | 3 | 1 | 0 | 0 | 14 | 0 | 0 | 0 | 0 |
| | (2.1) | (0.9) | (0.3) | (0.0) | (0.0) | (4.2) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain: Perineum | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain: Urethra | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| | (0.9) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) |
| Pain - Other | 5 | 0 | 2 | 0 | 0 | 11 | 3 | 0 | 0 | 0 |
| | (1.5) | (0.0) | (0.6) | (0.0) | (0.0) | (3.3) | (0.9) | (0.0) | (0.0) | (0.0) |
| **Sexual/Reproductive Function** | **7** | **2** | **0** | **0** | **0** | **16** | **3** | **0** | **0** | **0** |
| | **(2.1)** | **(0.6)** | **(0.0)** | **(0.0)** | **(0.0)** | **(4.8)** | **(0.9)** | **(0.0)** | **(0.0)** | **(0.0)** |
| Libido | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Vaginal Dryness | 2 | 2 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.6) | (0.0) | (0.0) | (0.0) | (1.8) | (0.3) | (0.0) | (0.0) | (0.0) |
| Vaginal Discharge | 4 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 |
| | (1.2) | (0.0) | (0.0) | (0.0) | (0.0) | (3.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Vaginitis | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | (0.6) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) | (0.0) |
| Sexual/Reproductive Function: Other | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) |
| **Syndromes** | **1** | **4** | **0** | **0** | **0** | **8** | **9** | **0** | **0** | **0** |
| | **(0.3)** | **(1.2)** | **(0.0)** | **(0.0)** | **(0.0)** | **(2.4)** | **(2.7)** | **(0.0)** | **(0.0)** | **(0.0)** |
| Flu-Like Syndrome | 1 | 0 | 0 | 0 | 0 | 7 | 7 | 0 | 0 | 0 |
| | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (2.1) | (2.1) | (0.0) | (0.0) | (0.0) |
| Cytokine Release Syndrome | 0 | 4 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) | (0.3) | (0.6) | (0.0) | (0.0) | (0.0) |
| **Vascular** | **0** | **2** | **2** | **2** | **0** | **2** | **8** | **10** | **4** | **0** |
| | **(0.0)** | **(0.6)** | **(0.6)** | **(0.6)** | **(0.0)** | **(0.6)** | **(2.4)** | **(3.0)** | **(1.2)** | **(0.0)** |
| Phlebitis | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.0) | (1.2) | (0.0) | (0.0) | (0.0) |
| Thrombosis/Thrombus/Embolism | 0 | 0 | 2 | 2 | 0 | 0 | 3 | 8 | 4 | 0 |
| | (0.0) | (0.0) | (0.6) | (0.6) | (0.0) | (0.0) | (0.9) | (2.4) | (1.2) | (0.0) |
| Thrombosis/Embolism (Vascular Access-Related) | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.3) | (0.3) | (0.0) | (0.0) |
| Artery Injury - Other | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Vein Injury - Extremity-Lower | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) |
| Vascular - Other | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| | (0.0) | (0.3) | (0.0) | (0.0) | (0.0) | (0.6) | (0.0) | (0.3) | (0.0) | (0.0) |

**Supplemental Table: Therapeutic Agents Used in the Next-line of Treatment (Overall Intention-To-Treat Population)**

| Response | Randomized Treatment | | | | |
|---|---|---|---|---|---|
| | CT N=337 | | CT+Bev N=337 | | Total N=674 |
| | N | % | N | % | N |
| None | 44 | 13.1 | 65 | 19.3 | 109 |
| bev | 17 | 5.0 | 8 | 2.4 | 25 |
| bev+cyt | 8 | 2.4 | 5 | 1.5 | 13 |
| bev+gem | 3 | 0.9 | . | . | 3 |
| bev+oth | 13 | 3.9 | . | . | 13 |
| bev+pem | 1 | 0.3 | . | . | 1 |
| bev+tax | 4 | 1.2 | 4 | 1.2 | 8 |
| bev+top | 1 | 0.3 | 1 | 0.3 | 2 |
| bev+xrt | 1 | 0.3 | . | . | 1 |
| cyt | 1 | 0.3 | . | . | 1 |
| cyt+oth | 1 | 0.3 | . | . | 1 |
| gem | 16 | 4.7 | 12 | 3.6 | 28 |
| gem+oth | 1 | 0.3 | . | . | 1 |
| hex | 1 | 0.3 | . | . | 1 |
| irn+oth | 1 | 0.3 | . | . | 1 |
| led | 50 | 14.8 | 54 | 16.0 | 104 |
| led+bev | 4 | 1.2 | 2 | 0.6 | 6 |
| led+gem | . | . | 1 | 0.3 | 1 |
| led+oth | 2 | 0.6 | . | . | 2 |
| led+plt | 6 | 1.8 | 13 | 3.9 | 19 |
| led+plt+oth | 1 | 0.3 | . | . | 1 |
| led+sur | . | . | 1 | 0.3 | 1 |
| ltr | 3 | 0.9 | 4 | 1.2 | 7 |
| ltr+tam | . | . | 1 | 0.3 | 1 |
| oth | 26 | 7.7 | 9 | 2.7 | 35 |
| oth+tam | . | . | 1 | 0.3 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| pem | 1 | 0.3 | 3 | 0.9 | 4 |
| plt | 8 | 2.4 | 12 | 3.6 | 20 |
| plt+bev | . | . | 1 | 0.3 | 1 |
| plt+bev+gem | 3 | 0.9 | 2 | 0.6 | 5 |
| plt+bev+tax | 2 | 0.6 | 4 | 1.2 | 6 |
| plt+gem | 25 | 7.4 | 31 | 9.2 | 56 |
| plt+gem+oth | . | . | 1 | 0.3 | 1 |
| plt+gem+sur | . | . | 1 | 0.3 | 1 |
| plt+oth | 7 | 2.1 | 1 | 0.3 | 8 |
| plt+sur | 1 | 0.3 | 1 | 0.3 | 2 |
| plt+tax | 21 | 6.2 | 33 | 9.8 | 54 |
| plt+tax+sur | . | . | 1 | 0.3 | 1 |
| plt+top | 4 | 1.2 | 4 | 1.2 | 8 |
| sur | 13 | 3.9 | 5 | 1.5 | 18 |
| sur+oth | . | . | 1 | 0.3 | 1 |
| sur+xrt | 1 | 0.3 | 1 | 0.3 | 2 |
| tam | 4 | 1.2 | 9 | 2.7 | 13 |
| tax | 11 | 3.3 | 12 | 3.6 | 23 |
| tax+gem | 1 | 0.3 | . | . | 1 |
| tax+irn | . | . | 1 | 0.3 | 1 |
| tax+oth | 7 | 2.1 | 8 | 2.4 | 15 |
| top | 12 | 3.6 | 16 | 4.7 | 28 |
| top+oth | 1 | 0.3 | . | . | 1 |
| xrt | 10 | 3.0 | 8 | 2.4 | 18 |

bev=bevacizumab; plt=platinum (carboplatin, cisplatin); tax=taxane (paclitaxel, taxotere, abraxane); gem=gemcitabine; led=liposomal doxorubicin or doxil; top=topotecan; cyt=cyclophosphamide; pem=pemetrexed; hex=hexamethylmelamine; tam=tamoxifen; sur=sunitinib; xrt=external beam radiation;oth=other;

**Supplemental Table: Summary of Cycles of Trial Treatment Received (Overall Safety Population)**

*The overall safety population represented here pertains to the treatment received by the study participant (as opposed to the Intention-To-Treat population). Five patients randomized to carboplatin, paclitaxel and bevacizumab did not receive bevacizumab. These patients are included in the cohort of patients receiving carboplatin and paclitaxel. Data cut-off: November 5, 2014.

| | Carboplatin+Paclitaxel (N=332)* | Carboplatin+Paclitaxel+Bevacizumab (N=325)* |
|---|---|---|
| Number of patients starting x cycles of Bevacizumab | | |
| 1-3 | 0 ( 0%) | 325 ( 100%) |
| 4-6 | 0 ( 0%) | 285 (87.7%) |
| 7-8 | 0 ( 0%) | 249 (76.6%) |
| 9-11 | 0 ( 0%) | 236 (72.6%) |
| 12-15 | 0 ( 0%) | 207 (63.7%) |
| >15 | 0 ( 0%) | 169 (52.0%) |
| Min-Max | | 1-111 |
| Mean | | 19.36 |
| Median | | 16 |
| Number of patients starting x cycles of Carboplatin | | |
| 1-3 | 332 ( 100%) | 325 ( 100%) |
| 4-6 | 277 (83.4%) | 295 (90.8%) |
| 7-8 | 141 (42.5%) | 148 (45.5%) |
| 9-11 | 15 ( 4.5%) | 3 ( 0.9%) |
| 12-15 | 3 ( 0.9%) | 2 ( 0.6%) |
| >15 | 1 ( 0.3%) | 0 ( 0%) |
| Min-Max | 1-20 | 1-13 |
| Mean | 6.26 | 6.44 |
| Median | 6 | 6 |
| Number of patients starting x cycles of Paclitaxel (or Docetaxel) | | |
| 1-3 | 332 ( 100%) | 325 ( 100%) |
| 4-6 | 286 (86.1%) | 303 (93.2%) |
| 7-8 | 144 (43.4%) | 155 (47.7%) |
| 9-11 | 19 ( 5.7%) | 7 ( 2.2%) |
| 12-15 | 5 ( 1.5%) | 1 ( 0.3%) |
| >15 | 1 ( 0.3%) | 0 ( 0%) |
| Min-Max | 1-16 | 1-13 |
| Mean | 6.41 | 6.61 |
| Median | 6 | 6 |
| Number of patients starting x cycles of All components of study medication | | |
| 1-3 | 332 ( 100%) | 325 ( 100%) |
| 4-6 | 277 (83.4%) | 279 (85.8%) |
| 7-8 | 139 (41.9%) | 128 (39.4%) |
| 9-11 | 14 ( 4.2%) | 1 ( 0.3%) |
| 12-15 | 3 ( 0.9%) | 1 ( 0.3%) |
| Min-Max | 1-14 | 1-12 |
| Mean | 6.21 | 6.00 |
| Median | 6 | 6 |

In the Carboplatin + Paclitaxel + Bevacizumab arm, the median total dose of bevacizumab was 16337.0 mg. In general, the median total doses of carboplatin and paclitaxel/docetaxel were comparable between the Carboplatin + Paclitaxel alone arm and the Carboplatin + Paclitaxel + Bevacizumab arm.

**Supplemental Table: Summary of Total Dose of Trial Treatment Received (Overall Safety Population)**

*The overall safety population represented here pertains to the treatment received by the study participant (as opposed to the Intention-To-Treat population). Five patients randomized to carboplatin, paclitaxel and bevacizumab did not receive bevacizumab. These patients are included in the cohort of patients receiving carboplatin and paclitaxel. Data cut-off: November 5, 2014.

| | Carboplatin+Paclitaxel (N=332)* | Carboplatin+Paclitaxel+Bevacizumab (N=325)* |
|---|---|---|
| Bevacizumab (mg) | | |
| Mean | | 21526.6 |
| SD | | 20400.74 |
| 25th percentile | | 7980.0 |
| Median | | 16337.0 |
| 75th percentile | | 29374.0 |
| Min | | 721.0 |
| Max | | 165200.0 |
| n | 0 | 325 |
| Carboplatin (mg) | | |
| Mean | 2958.3 | 3055.4 |
| SD | 1211.92 | 1029.79 |
| 25th percentile | 2343.0 | 2412.0 |
| Median | 3031.0 | 3230.0 |
| 75th percentile | 3670.5 | 3736.0 |
| Min | 373.0 | 309.0 |
| Max | 10700.0 | 5800.0 |
| n | 332 | 325 |
| Paclitaxel (mg) | | |
| Mean | 1883.9 | 1952.8 |
| SD | 663.08 | 564.39 |
| 25th percentile | 1581.0 | 1662.0 |
| Median | 1917.0 | 1999.0 |
| 75th percentile | 2307.8 | 2360.0 |
| Min | 267.0 | 277.0 |
| Max | 4800.0 | 3280.0 |
| n | 324 | 314 |
| Docetaxel (mg) | | |
| Mean | 509.3 | 551.2 |
| SD | 343.29 | 290.41 |
| 25th percentile | 232.0 | 279.0 |
| Median | 450.0 | 600.9 |
| 75th percentile | 700.0 | 755.5 |
| Min | 118.0 | 118.5 |
| Max | 1200.0 | 1140.0 |
| n | 21 | 20 |

The median dose intensity calculated as the actual dose administered divided by the planned dose, based on the patients baseline weight, for bevacizumab in the Carboplatin + Paclitaxel + Bevacizumab arm was 93.9%.

The median dose intensity for carboplatin was 85.7% in the Carboplatin + Paclitaxel alone arm and 86.5% in the Carboplatin + Paclitaxel + Bevacizumab arm and for paclitaxel/docetaxel was 92.3% in the Carboplatin + Paclitaxel alone arm and 91.0% in the Carboplatin + Paclitaxel + Bevacizumab arm. The median dose intensity of bevacizumab was 93.9%. The percentage of patients who received at least 90% of the planned number of doses of trial treatment was similar in the Carboplatin + Paclitaxel alone arm (16.6%) and in the Carboplatin + Paclitaxel +

Bevacizumab arm (19.7%). At least one dose of carboplatin was missed by 30.4% of patients in the Carboplatin + Paclitaxel alone arm and by 28.6% of patients in the Carboplatin + Paclitaxel + Bevacizumab arm; 30.1% and 27.1% of patients in the Carboplatin + Paclitaxel alone and Carboplatin + Paclitaxel + Bevacizumab arms, respectively, missed at least one dose of paclitaxel/docetaxel. At least one dose of bevacizumab was missed by 48.3% of patients.

**Supplemental Table: Summary of Dose Intensity and Missed or Delayed Doses by Trial Treatment (Overall Safety Population)**

*The overall safety population represented here pertains to the treatment received by the study participant (as opposed to the Intention-To-Treat population). Five patients randomized to carboplatin, paclitaxel and bevacizumab did not receive bevacizumab. These patients are included in the cohort of patients receiving carboplatin and paclitaxel. Data cut-off: November 5, 2014.

| | Carboplatin+Paclitaxel (N=332)* | Carboplatin+Paclitaxel+Bevacizumab (N=325)* |
|---|---|---|
| **Treatment: BEVACIZUMAB** | | |
| Dose Intensity (%) | | |
| Mean | | 92.3 |
| 25th percentile | | 88.8 |
| Median | | 93.9 |
| 75th percentile | | 97.5 |
| Min | | 58.0 |
| Max | | 122.1 |
| All Missed/Delayed doses | | |
| n with at least one missed/delayed dose | 0 (0.0%) | 157 (48.3%) |
| 1 dose | 0 (0.0%) | 72 (22.2%) |
| 2 doses | 0 (0.0%) | 37 (11.4%) |
| 3 doses | 0 (0.0%) | 24 (7.4%) |
| >3 doses | 0 (0.0%) | 24 (7.4%) |
| **Treatment: CARBOPLATIN** | | |
| Dose Intensity (%) | | |
| Mean | 85.2 | 86.6 |
| 25th percentile | 74.3 | 74.7 |
| Median | 85.7 | 86.5 |
| 75th percentile | 96.4 | 99.4 |
| Min | 31.3 | 31.4 |
| Max | 126.5 | 143.7 |
| All Missed/Delayed doses | | |
| n with at least one missed/delayed dose | 101 (30.4%) | 93 (28.6%) |
| 1 dose | 65 (19.6%) | 70 (21.5%) |
| 2 doses | 31 (9.3%) | 18 (5.5%) |
| 3 dose missed | 4 (1.2%) | 3 (0.9%) |
| >3 doses | 1 (0.3%) | 2 (0.6%) |
| **Treatment: PACLITAXEL or DOCETAXEL** | | |
| Dose Intensity (%) | | |
| Mean | 88.3 | 88.0 |
| 25th percentile | 80.0 | 81.2 |
| Median | 92.3 | 91.0 |
| 75th percentile | 97.9 | 97.5 |
| Min | 51.1 | 20.6 |
| Max | 108.4 | 104.0 |
| All Missed/Delayed doses | | |
| n with at least one missed/delayed dose | 100 (30.1%) | 88 (27.1%) |
| 1 dose | 64 (19.3%) | 65 (20.0%) |
| 2 doses | 32 (9.6%) | 17 (5.2%) |
| 3 doses | 2 (0.6%) | 4 (1.2%) |
| >3 doses | 2 (0.6%) | 2 (0.6%) |
| No. of Pts. with at least 90% of planned dose received | 55 (16.6%) | 64 (19.7%) |

**Supplemental Table: Summary of PFS by Stratification Variables (Overall ITT Population)**

| | | Carboplatin + Paclitaxel | | | Carbo + Pac + Bev | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subgroup | | N | Events | Median | N | Events | Median | HR | 95% CI |
| OB2 (surgery) | Yes | 54 | 48 | 14.2 | 53 | 38 | 18.7 | 0.57 | 0.37,0.89 |
| | NO | 282 | 257 | 9.8 | 284 | 260 | 13.6 | 0.64 | 0.54,0.77 |
| | | | | | | | | | |
| PFI (months)* | 6-12 | 83 | 77 | 8.3 | 91 | 87 | 10.5 | 0.68 | 0.50,0.92 |
| | >12 | 253 | 228 | 11.0 | 246 | 211 | 15.0 | 0.62 | 0.51,0.74 |
| | | | | | | | | | |
| Prior Bevacizumab | Yes | 34 | 31 | 9.8 | 35 | 34 | 10.7 | 0.84 | 0.52,1.37 |
| | No | 285 | 259 | 10.2 | 299 | 263 | 13.8 | 0.63 | 0.53,0.75 |

*PFI represents the corrected and audited platinum-free interval (see text for details)

**Supplemental Table: Summary of adverse events leading to treatment discontinuation (Overall Safety Population).**

*The overall safety population represented here pertains to the treatment received by the study participant (as opposed to the Intention-To-Treat population). Five patients randomized to carboplatin, paclitaxel and bevacizumab did not receive bevacizumab. These patients are included in the cohort of patients receiving carboplatin and paclitaxel. Data cut-off: November 5, 2014.

| Body System/ Adverse Event | Crb+Pac N = 332* No. (%) | Crb+Pac+Bev N = 325* No. (%) |
|---|---|---|
| ALL BODY SYSTEMS | | |
| Total Pts with at Least one AE | 37 ( 11) | 82 ( 25) |
| Total Number of AEs | 39 | 90 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Total Pts With at Least one AE | 14 ( 4) | 18 ( 6) |
| ADVERSE DRUG REACTION | 9 ( 3) | 3 ( <1) |
| UNEVALUABLE EVENT | 3 ( <1) | 9 ( 3) |
| ADVERSE EVENT | 1 ( <1) | 1 ( <1) |
| FATIGUE | - | 2 ( <1) |
| ADVERSE REACTION | - | 1 ( <1) |
| GENERAL PHYSICAL HEALTH DETERIORATION | 1 ( <1) | - |
| HERNIA | - | 1 ( <1) |
| THROMBOSIS IN DEVICE | - | 1 ( <1) |
| Total Number of AEs | 14 | 18 |
| INVESTIGATIONS | | |
| Total Pts With at Least one AE | 6 ( 2) | 19 ( 6) |
| URINE PROTEIN/CREATININE RATIO INCREASED | - | 9 ( 3) |
| UNEVALUABLE INVESTIGATION | 1 ( <1) | 5 ( 2) |
| NEUTROPHIL COUNT DECREASED | 2 ( <1) | 2 ( <1) |
| PLATELET COUNT DECREASED | 2 ( <1) | 1 ( <1) |
| BLOOD COUNT ABNORMAL | 1 ( <1) | - |
| BLOOD CREATININE INCREASED | - | 1 ( <1) |
| BLOOD PRESSURE INCREASED | - | 1 ( <1) |
| Total Number of AEs | 6 | 19 |
| IMMUNE SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 12 ( 4) | 5 ( 2) |
| DRUG HYPERSENSITIVITY | 8 ( 2) | 2 ( <1) |
| HYPERSENSITIVITY | 3 ( <1) | 3 ( <1) |
| ANAPHYLACTIC REACTION | 1 ( <1) | - |
| Total Number of AEs | 12 | 5 |
| NERVOUS SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 3 ( <1) | 7 ( 2) |
| NEUROPATHY PERIPHERAL | 1 ( <1) | 2 ( <1) |
| CEREBRAL ISCHAEMIA | 1 ( <1) | 1 ( <1) |
| CEREBROVASCULAR ACCIDENT* | 1 ( <1)* | - |
| DEMENTIA | - | 1 ( <1) |
| HAEMORRHAGE INTRACRANIAL* | - | 1 ( <1)* |
| HEADACHE | - | 1 ( <1) |
| SEIZURE | - | 1 ( <1) |
| TRANSIENT ISCHAEMIC ATTACK | - | 1 ( <1) |
| Total Number of AEs | 3 | 8 |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |

| | | |
|---|---|---|
| Total Pts With at Least one AE | 2 ( <1) | 7 ( 2) |
| NEUTROPENIA | 2 ( <1) | 3 ( <1) |
| THROMBOCYTOPENIA | - | 4 ( 1) |
| HAEMATOTOXICITY | - | 1 ( <1) |
| Total Number of AEs | 2 | 8 |
| GASTROINTESTINAL DISORDERS | | |
| Total Pts With at Least one AE | 2 ( <1) | 7 ( 2) |
| SMALL INTESTINAL OBSTRUCTION | - | 2 ( <1) |
| COLITIS | - | 1 ( <1) |
| GASTROINTESTINAL FISTULA | - | 1 ( <1) |
| GINGIVAL BLEEDING | - | 1 ( <1) |
| LARGE INTESTINAL OBSTRUCTION | 1 ( <1) | - |
| NAUSEA | 1 ( <1) | - |
| SMALL INTESTINAL PERFORATION | - | 1 ( <1) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | - | 1 ( <1) |
| Total Number of AEs | 2 | 7 |
| RENAL AND URINARY DISORDERS | | |
| Total Pts With at Least one AE | - | 8 ( 2) |
| PROTEINURIA | - | 8 ( 2) |
| Total Number of AEs | - | 8 |
| CARDIAC DISORDERS | | |
| Total Pts With at Least one AE | - | 3 ( <1) |
| ACUTE CORONARY SYNDROME | - | 1 ( <1) |
| ACUTE MYOCARDIAL INFARCTION | - | 1 ( <1) |
| MYOCARDIAL INFARCTION | - | 1 ( <1) |
| Total Number of AEs | - | 3 |
| VASCULAR DISORDERS | | |
| Total Pts With at Least one AE | - | 3 ( <1) |
| HYPERTENSION | - | 3 ( <1) |
| Total Number of AEs | - | 3 |
| INFECTIONS AND INFESTATIONS | | |
| Total Pts With at Least one AE | - | 2 ( <1) |
| HERPES ZOSTER | - | 1 ( <1) |
| PELVIC ABSCESS | - | 1 ( <1) |
| Total Number of AEs | - | 2 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 2 ( <1) |
| ARTHRALGIA | - | 2 ( <1) |
| Total Number of AEs | - | 2 |
| PSYCHIATRIC DISORDERS | | |
| Total Pts With at Least one AE | - | 2 ( <1) |
| DEPRESSION SUICIDAL | - | 1 ( <1) |
| MENTAL STATUS CHANGES | - | 1 ( <1) |
| Total Number of AEs | - | 2 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| Total Pts With at Least one AE | - | 2 ( <1) |
| PULMONARY EMBOLISM | - | 2 ( <1) |
| Total Number of AEs | - | 2 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | |
| Total Pts With at Least one AE | - | 1 ( <1) |
| TOXICITY TO VARIOUS AGENTS | - | 1 ( <1) |
| Total Number of AEs | - | 1 |

| | | |
|---|---|---|
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 1 ( <1) |
| SKIN ULCER | - | 1 ( <1) |
| Total Number of AEs | - | 1 |
| SOCIAL CIRCUMSTANCES | | |
| Total Pts With at Least one AE | - | 1 ( <1) |
| REFUSAL OF TREATMENT BY PATIENT | - | 1 ( <1) |
| Total Number of AEs | - | 1 |

There was 1 cases of intracranial hemorrhage observed that led to treatment discontinuation:

**Patient summary:** This 62-year-old, Asian female was diagnosed with Stage IIIC poorly differentiated endometrioid ovarian cancer and underwent primary debulking surgery with exploratory laparotomy, bilateral salpingo-oophorectomy followed by 6 cycles of paclitaxel/cisplatin. Following this, she then underwent interval debulking surgery with exploratory laparotomy, total abdominal hysterectomy, omentectomy, and pelvic and para-aortic lymph nodes dissection followed by 6 cycles of adjuvant paclitaxel/carboplatin. She was diagnosed with disease recurrence 31 months later. At enrollment, the patient's GOG performance status was 1. No other medical history was reported. A screening CT showed measureable disease with lymph node metastases. The patient was enrolled in Study GOG-0213 and randomized to carboplatin + paclitaxel + bevacizumab. She received a total of 6 cycles of chemotherapy and 8 cycles of bevacizumab prior to the event onset. On treatment Day 177, the patient reported unspecified symptoms. She was hospitalized at regional clinic and work-up included brain imaging which showed intracranial hematoma and the patient was diagnosed with Grade 4 intracranial hemorrhage. The hematoma was surgically removed on same day. On treatment Day 223, she was transferred to a sub-acute rehabilitation center for rehabilitation for right sided paralysis and aphasia. On treatment Day 404, the event of intracranial hemorrhage was considered resolved with sequelae. The same day (Day 404), she was discharged from sub-acute rehabilitation hospital and was recuperating at home. It was reported that she was then able to take care of herself and talk clearly although the speed was slow. Due to intracranial hemorrhage, study treatment was permanently discontinued with the last cycle of bevacizumab-administered treatment Day 174. The patient received a total of 6 cycles of carboplatin and paclitaxel and 8 cycles of bevacizumab on study. The investigator considered intracranial hemorrhage related to bevacizumab and unrelated to carboplatin and paclitaxel. No other possible etiological factors reported. On treatment Day 1126, the patient was diagnosed with disease progression. She was reported as alive at the time of last follow-up.

## Supplemental Table: Protocol Violations (ITT Population)

| | Crb+Pac (N=337) | | Crb+Pac+Bev (N=337) | |
|---|---|---|---|---|
| Violation | | | | |
| MAJOR VIOLATION | 16 | ( 4.8%) | 17 | ( 5.0%) |
| MINOR VIOLATION | 27 | ( 8.0%) | 14 | ( 4.2%) |
| Results of pathology committee review of patient eligibility for protocol and tumor grade | | | | |
| WELL DIFFERENTIATED | 17 | ( 5.1%) | 20 | ( 5.9%) |
| MODERATELY DIFFERENTIATED | 44 | (13.1%) | 53 | (15.7%) |
| POORLY DIFFERENTIATED | 253 | (75.3%) | 249 | (73.9%) |
| NOT GRADED | 11 | ( 3.3%) | 7 | ( 2.1%) |
| EXCLUSION | 11 | ( 3.3%) | 8 | ( 2.4%) |
| Results of gynecologic committee review of patient eligibility | | | | |
| ACCEPT | 309 | (92.0%) | 304 | (90.2%) |
| Reason for exclusion from protocol | | | | |
| ADDITIONAL THERAPY WITHOUT RECURRENCE | 1 | ( 0.3%) | 0 | ( 0.0%) |
| INADEQUATE PATHOLOGY | 8 | ( 2.4%) | 3 | ( 0.9%) |
| WRONG CELL TYPE | 3 | ( 0.9%) | 2 | ( 0.6%) |
| WRONG PRIMARY | 0 | ( 0.0%) | 3 | ( 0.9%) |

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PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

*NCI Version 9/12/07*

POINTS:

PER CAPITA –30

MEMBERSHIP –6 and 6 additional if patient is randomized to surgical arm.

TRANSLATIONAL RESEARCH PER CAPITA – Award up to 6 points based on specimen submissions.
Distribution:

- Archival fixed and embedded primary or metastatic tumor (block or 16 unstained slides)-1 point,
- Frozen recurrent or persistent tumor-1 point
- Fixed recurrent tumor in formalin-1 point
- Frozen normal tissue-0.5 point
- Fixed normal tissue in formalin-0.5 point
- Frozen pre-op serum-0.5 point
- Frozen pre-op plasma-0.5 point

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for **submission of satisfactory** fixed primary tumor, frozen recurrent or persistent tumor, fixed recurrent or persistent tumor, frozen serum and frozen plasma.

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PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

*NCI Version: 9/12/07*

POINTS:
PER CAPITA-30
MEMBERSHIP-6

**Patient enrollments from U.S. Cooperative Group clinical sites not aligned with GOG, will be conducted via the Cancer Trials Support Unit (CTSU) and all data should be sent to the CTSU**



Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
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Phone: 1-888-823-5923
Fax – 215-569-0206

CTSU Data Operations Center
Phone – 1-888-462-3009
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CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062

**All other questions (including forms-specific questions) should be communicated by phone or e-mail to:**
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

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**CTSU logistical information is found in Appendix II.**

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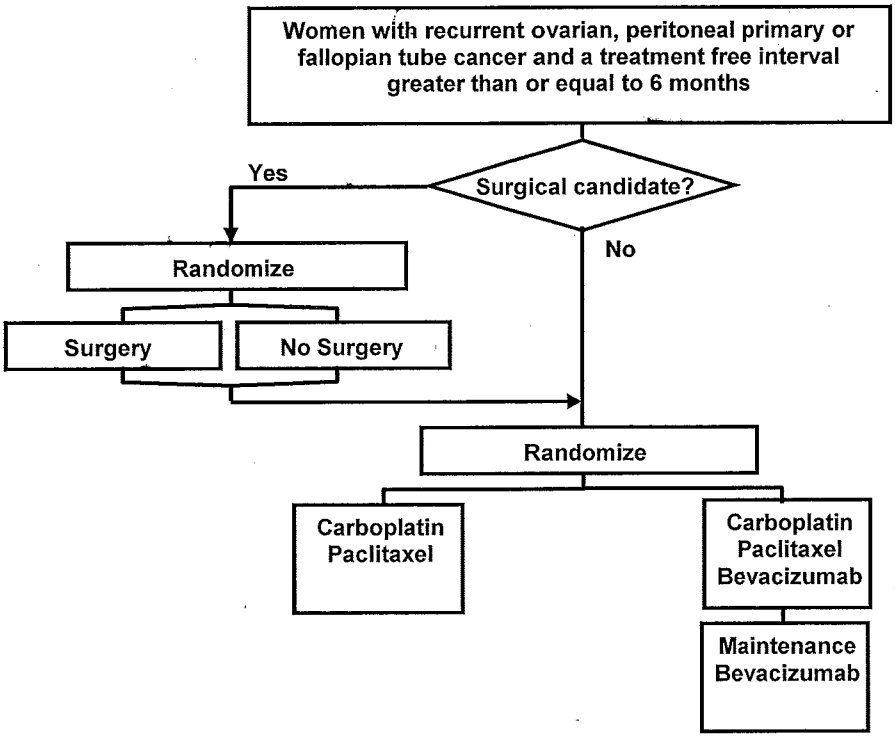
SCHEMA




The translational research component of GOG-0213 will focus on patients who are randomized to have secondary cytoreductive surgery and give permission for their tissue and/or serum to be used for this research study as described in Section 7.2.

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## 1.0 OBJECTIVES

Specific Hypotheses:

Two principle hypotheses will be directly addressed in this randomized, phase III clinical trial in recurrent platinum-sensitive ovarian and peritoneal primary cancer patients.

1.11 Surgical secondary cytoreduction prior to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.12 The addition of bevacizumab to second-line paclitaxel and carboplatin and maintenance phases of treatment increases the duration of overall survival relative to second-line chemotherapy alone in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.2 Primary Objectives:

1.21 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.22 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of overall survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.3 Secondary objectives:

1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.

1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

1.34 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases QOL relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer or peritoneal primary cancer.

1.4 Translational Research Hypotheses

The following translational research hypotheses will be tested in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.

1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian or peritoneal primary carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.5 Translational Research Objectives

The following translational research objectives will be evaluated in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian or peritoneal primary carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.

1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.

## 2.0 BACKGROUND AND RATIONALE

### 2.1 Rationale for Selected Approach and Trial Design

Ovarian cancer remains the most lethal primary gynecologic malignancy in the United States. This year over 16,000 women will die from their disease. The principle reason for this outcome is disease recurrence and the emergence of drug resistance. Patients with recurrent disease frequently undergo multiple cycles of multiple drug regimens. Those fortunate to achieve a response to chemotherapy are however, rarely cured and find that their remission cycles are short-lived. Even if a complete response is re-achieved it is usually of a shorter duration than the first disease-free interval. Those not achieving a response to recurrence therapy live less than 2 years. While effective therapy following disease recurrence is a major unmet need, few interventions have successfully altered the natural history of recurrence. We propose to address two important interventions, surgery and combination chemotherapy with biologics, neither previously studied in a prospective randomized design, in order to determine their impact on survival.

2.2 Rationale for Surgery

The capacity of cytoreductive surgery to improve survival for patients with advanced, newly diagnosed epithelial ovarian cancer is generally accepted.[1] However, the role of tumor-reductive surgery for patients with recurrent disease continues to evolve.[2] Several series have demonstrated the importance of tumor reductive surgery prior to the initiation of second-line chemotherapy.[1, 3, 4] Preliminary results indicate a maximal survival benefit for patients rendered visibly disease-free prior to second-line therapy.[1, 4, 5] The frequency of reported optimal operative outcomes has ranged from 37% to 83% in small series, using various criteria for "optimal cytoreduction".[6] The relative importance that differences in study cohorts, attitude, technical capability and experience have in accounting for variation of operative outcomes is unknown. In a recent series, the largest yet published, approximately 80% of the patients had complete cytoreduction.[5] Clinical criteria such as the median age, median disease-free interval, amount of prior chemotherapy, performance status, size of intra-abdominal disease, and locations of disease suggests patients in that series to have disease at least as advanced as other reports.[1, 3, 4, 7] That investigation prospectively demonstrated that secondary cytoreductive surgery, followed by salvage chemotherapy, allows survival that is significantly improved. The 34.4 month overall median survival from the time of secondary operation and the 35.9 month overall median survival from the time of recurrence in the most recent series exceed what is typically reported in the salvage chemotherapy literature. Another noteworthy observation from this study was that the median survival after diagnosis of recurrence for patients who did not have salvage chemotherapy before secondary operation (48.4 months) dramatically exceeded the overall median survival for those who were pretreated (24.9 months). Furthermore, an estimated 40% of the patients operated on before administration of salvage therapy survived more than five years after recurrence compared to only 15% in the pretreated group. Of note, patients whose disease responded to a recent repeat course of platinum containing agents, and patients treated with non-platinum containing agents before secondary operation, both had poor survival, that did not remotely approach the overall group who had secondary cytoreductive operations prior to salvage chemotherapy. Perhaps pretreatment with salvage chemotherapy induces drug resistance. Regardless, limiting the role of surgery to palliation of symptoms for patients who failed multiple salvage regimens and the strategy of treating with salvage chemotherapy before an attempt at secondary cytoreductive surgery may greatly diminish the chances for subsequent survival. Confirmation of this observation within the context of a multi-center randomized trial may dramatically improve the survival potential for women with recurrent epithelial ovarian cancer.

2.3 Rationale for Combination Chemotherapy

Most patients medically suitable to undergo therapy at the time of recurrence will be offered chemotherapy. To date, a limited number of agents (i.e. etoposide, liposomal doxorubicin, topotecan, etc) have been formally approved for administration in this setting. In addition, several other agents have been studied and are documented to have clinical activity. Joining these novel agents are the taxanes and platinates commonly used as standard therapy in the front-line setting. In light of this expansion of potentially active chemotherapeutics, physicians are administering more agents, longer to more patients. Nonetheless, the degree to which this practice is benefiting patients in terms of survival is unclear.

An additional challenge lies in how to determine when to recommend which agents or combinations to patients with recurrent disease. A common determinant for many clinicians lies in reference to the patient's time in remission following front-line therapy. Those disease-free for more than six months are commonly considered to be potentially sensitive to retreatment with platinum. Response characteristics with single agent platinum in this setting produce results similar to patients treated with novel agents. Patients with longer disease-free interval are commonly treated with combination platinum and taxane therapy similar to the regimens received as primary therapy. The degree to which this philosophy of care has affected survival is unknown but data from the limited number of randomized trials would suggest the following:

- Non-platinum novel agents such as topotecan, liposomal doxorubicin, and paclitaxel have similar response and survival characteristics as compared to platinum in randomized phase III trials.
- No difference in response has been observed in these novel agents among platinum sensitive or resistant patients. However, treatment with liposomal doxorubicin demonstrated a survival benefit in comparison to topotecan in the absence of a response benefit among patients with platinum-sensitive disease.[8] The reasons for this are not clear but may relate to either intrinsic drug activity or to trial design (limited availability to liposomal doxorubicin in topotecan failures).
- Platinum and platinum/taxane combinations have favorable response characteristics in platinum-sensitive patients.[9, 10] Platinum and taxane combination therapy appears to be at least as effective as single agent platinum and data from one large phase III trial would suggest clinical superiority.[11] Although the randomized population in that trial was dissimilar to those commonly treated in the US, a second randomized phase II clinical trial in a more selective population essentially confirmed the observed benefit.[12] Further, a randomized clinical trial of gemcitabine and carboplatin demonstrated superiority in progression-free survival over carboplatin alone in platinum-sensitive patients.[13] Although a survival benefit was not demonstrated, the trial was underpowered to address this endpoint.

  From these observations, it would appear the greatest activity and potential for survival enhancement lies in combination, platinum-based chemotherapy among those deemed potentially platinum (and taxane) sensitive. As demonstrated above, a survival benefit is also suspected in this cohort for surgery. A randomized trial is needed to evaluate the addition of surgery to combination therapy to determine their impact on survival.

2.31 **Docetaxel**

Taxanes are a class of anticancer agents that exert cytotoxic effects by their unique inhibition of microtubular assembly by stabilizing tubulin polymer bundles.[14, 15] Both paclitaxel and docetaxel belong to the taxane family and have demonstrated activity in tumors that are refractory to conventional chemotherapy regimens. Paclitaxel is a diterpene plant product derived from the bark of the Western yew (Taxus brevifolia), while docetaxel is a semisynthetic derivative of 10-deacetylbaccatin III, a compound extracted from the needles of the European yew (Taxus baccata). While the relative efficacy of paclitaxel and docetaxel has not been compared clinically, docetaxel has increased activity in vitro, as well as clinical activity in paclitaxel resistant tumors.

**In Vitro Activity.**
The cytotoxicity of docetaxel in comparison with paclitaxel was evaluated in several murine and human long-term cell culture lines. Docetaxel was found to be generally more cytotoxic (1.3-12-fold), a result that could be explained by its higher achievable intracellular concentration, its higher affinity for microtubules, and its slower cellular efflux.[14-21] Furthermore, docetaxel affects centromere organization resulting in abortive mitosis.[22] These cellular events may account for the greater cytotoxicity of docetaxel compared to that seen with paclitaxel. In terms of cross-resistance with other antitumor agents, there was cross-resistance to docetaxel in multidrug-resistant sublines such as P388/DOX3, CEM/VLB 1000 and Chinese hamster ovary AUXB1 line.[23] However, no cross-resistance to docetaxel was observed in CHO cells expressing a low level of vincristine-resistance but P-glycoprotein positive.[23] This means that cross-resistance to docetaxel was not definitively observed in sublines expressing the MDR phenotype.[24] These findings were in agreement with cell line studies showing that docetaxel was active in paclitaxel-resistant cells.[16] In addition, there was a lack of cross-resistance to cisplatin in certain cell lines.[17,22]

**Efficacy in Murine Tumor Models**
In a murine tumor model with B16 melanoma, docetaxel demonstrated clear superiority to paclitaxel, having a 2.7 times greater log cell kill than paclitaxel.[25] Docetaxel at a dose of 100 mg/ $m^2$ has demonstrated significant activity with response rates of 23-40% as second-line therapy in platinum resistant ovarian carcinoma.[26-28] More recently, its activity in paclitaxel-resistant tumors has been studied. The use of docetaxel at a dose of 100 mg/ $m^2$ every 21 days in paclitaxel-resistant breast cancer has demonstrated a 17.5% response rate in 41 evaluable patients.[29] Additionally, the use of docetaxel at this same dose in paclitaxel-resistant ovarian cancer has recently demonstrated a 37.5% response rate in 8 evaluable patients.[30] The in vitro, in vivo and clinical data make docetaxel an excellent agent to evaluate after primary platinum and paclitaxel therapy. Hematologic toxicity is the dose-limiting toxicity, with neutropenic fever occurring in 8- 48% of patients.[26-28] Hematologic toxicity is considerably more severe with poorer hepatic function.[31] A comparative study of patients with or without liver dysfunction treated with docetaxel at a dose of 100 mg/ $m^2$ was recently reported. Patients with impaired liver function defined as an SGOT or SGPT > 1.5 x upper limit of normal or alkaline phosphatase > 2.5 x upper limit of normal, had a higher rate of neutropenic fever 23.8% vs 12.9% (p=0.06) and toxic death 11.9% vs 1.7%, (p=0.001). For that reason strict criteria for hepatic function are required for this study.

**Efficacy in Humans**
Several phase II and one randomized phase III trial have been conducted evaluating clinical efficacy of docetaxel in primary and recurrent ovarian cancer. Rose et al., reporting on behalf of the GOG, demonstrated a 22.4% overall response rate (5% CR and 17% PR) in 60 patients with platinum and taxane resistant recurrent disease (defined as progression on or within 6 months of completion of primary therapy). Docetaxel for this trial was administered at 100 mg/ $m^2$. Grade IV hematologic toxicity was observed in 75% of patients at this dose.[32] Similarly, Verschraegen et al., reported a 23% response rate and a

median PFS of 3.5 months among 30 assessable patients in a slightly less resistant population. Grade IV granulocytopenia occurred in 72% of protocol patients and like the Rose trial was a reflection of higher docetaxel dosing (100 mg/ $m^2$).[30] Markman, evaluated docetaxel (75 mg/ $m^2$) in 30 taxane-resistant ovarian cancer patients. In this study, taxane-resistance was defined as progression on or within 3 months of paclitaxel therapy. Patients with longer intervals from paclitaxel were to be retreated with that agent – and progressed – prior to docetaxel. In this trial, 3 patients (10%) had an objective response. Hematologic toxicity was reduced (30%, Grade IV), likely a reflection of reduced dosing.[33]

Based on objective clinical activity in these resistant patient cohorts, a randomized clinical trial comparing taxane and platinum combination therapy in front line ovarian cancer treatment was conducted and recently reported. Vasey and colleagues reported similar PFS (15.0 vs 14.8 months, HR: 0.97 (0.83-1.13) and OS rate at 24 months (64.2% vs. 68.9%, HR: 1.13 (0.92-1.39) for the docetaxel/carboplatin combination compared with the industry standard paclitaxel/carboplatin. In this 1077 patient trial toxicity was significantly different with more hematological toxicity seen in the docetaxel combination (Grade III/IV granulocytopenia 94% vs. 84%, $P < 0.001$) but more severe and longer lasting sensory-motor neurotoxicity for paclitaxel/carboplatin (11% vs. 30, $P < 0.001$).[34] These trials establish clinical efficacy and safety for docetaxel and suggest possible non-cross resistance with paclitaxel. Given the lack of a clear dose response for this agent we propose to utilize 75 mg/ $m^2$ to initiate the trial.

## 2.4 Rationale for Angiogenesis Targeted Therapy

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells and normal endothelial cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[35-38] A strong relationship exists between the expression of angiogenesis biomarkers and the behavior of epithelial ovarian cancer, suggesting pharmacological inhibitors of angiogenesis could arrest tumor progression.[39, 40] Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[41] Bevacizumab is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, named rhuMAb VEGF. Bevacizumab has been advanced into clinical development for use as a single agent to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to disease progression in patients with metastatic solid tumors.[42] A recent phase II trial of single agent bevacizumab for patients with recurrent, platinum/taxane refractory epithelial ovarian and peritoneal primary cancer has been reported in the GOG (GOG-0170D). Sixty-two women were enrolled in the phase II trial, and objective responses were observed in 17.7%.[43] Response duration was 10.3 months. This was an extremely unusual observation for a compound presumed to be at best cytostatic when administered as a single agent. Further exploration in combination with chemotherapy

is warranted in ovarian cancer patients given the survival benefits observed for bevacizumab-combinations in other solid tumors such as breast, renal, lung and colon cancers.

## 2.5 Rationale for Combination Cytotoxic and Biologic Therapy

Evidence from pre-clinical studies and recent phase II and III clinical trials in other solid tumors has demonstrated enhanced anti-tumor activity of traditional cytotoxic regimens, when combined with bevacizumab. For example, Devore and colleagues reported on a three-arm phase II randomized trial of carboplatin/paclitaxel with or without bevacizumab (7.5 mg/kg or 15 mg/kg dose levels) every 21 days until disease progression, in 99 patients with stages IIIB and IV non-small cell lung cancer. Response rates were 21.9 percent (7/32 patients) in the low dose and 42.9 percent (14/35 patients) in the high dose bevacizumab combination arms, compared to a response rate of 31.3 percent (10/32 patients) in the chemotherapy alone arm. A phase II/III trial in this patient population has been conducted by ECOG; the final analysis of this study is pending.

More importantly, a recently reported phase III trial, AVF2107, of over 800 previously untreated patients with metastatic colorectal cancer randomized to receive either bevacizumab for one year plus the Saltz chemotherapy regimen (5-FU/Leucovorin/CPT-11, IFL) or the Saltz regimen plus placebo for one year met its primary endpoint of improving overall survival. The magnitude of benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary endpoints of progression-free survival, response rate, and duration of response (see following table).

| | **IFL/Bevacizumab (n = 403)** | **IFL/Placebo (n = 412)** | **Hazard Ratio (p-value)** |
|---|---|---|---|
| Response Rate | 44.9% | 34.7% | (0.0029) |
| Median TTP | 10.6 mos | 6.2 mos | (0.00001) |
| Median Survival | 20.3 mos | 15.6 mos | 0.65 (0.00003) |

Bleeding, thrombosis, asymptomatic proteinuria and hypertension were identified in phase II studies as possible safety events, but only Grade 3 hypertension and arterial thrombosis events were clearly increased in this phase III study.

Preliminary results from a more recent, large, randomized phase III trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab in combination with an oxaliplatin regimen known as FOLFOX4 (oxaliplatin, 5-fluorouracil and leucovorin) had a significantly prolonged survival over patients who received FOLFOX4 alone. The Data Monitoring Committee overseeing the trial, known as E3200, recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival, which was 17% longer in the bevacizumab arm. Specifically, the median overall survival in the bevacizumab plus FOLFOX4 arm was 12.5 months compared to 10.7 months for patients treated with FOLFOX4 alone. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients

in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone. Treatment toxicities observed in this study were consistent with those adverse effects observed in other clinical trials in which bevacizumab was combined with chemotherapy. These included hypertension and bleeding as more predominant in the bevacizumab arm.

Multiple phase I-III trials, such as those cited above, have demonstrated the safety and tolerability of bevacizumab with traditional schedules and dosing of carboplatin and paclitaxel.

2.6 Gastrointestinal Perforation/Fistula

GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. In various phase II series of bevacizumab in recurrent ovarian cancer the rate of GI perforation has ranged from 0-14%. No phase III randomized trials of bevacizumab alone or in combination with chemotherapy have been conduct heretofore. Review of cases reported to CTEP in an open-label phase II ovarian cancer trial of bevacizumab did not specifically isolate risk factors for this complication; however, most patients were heavily pretreated and had abdominal tumor burden (CTEP IND Action Letter, October 4, 2005). GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, or comorbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

2.7 Rationale for Clinical Trial Design

Bevacizumab was selected for evaluation in combination with standard chemotherapy based on preliminary phase II single agent data obtained in patients with recurrent epithelial ovarian and peritoneal primary cancers and results from a phase III clinical trial in patients with metastatic colorectal cancer demonstrating a survival benefit to patients receiving bevacizumab with standard cytotoxic chemotherapy compared with patients receiving standard chemotherapy alone. Based on the mechanism of action of bevacizumab, there may be benefit to extended therapy until disease progression, in extending PFS or OS in this patient population. Therefore, combination chemotherapy is compared against combination carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance therapy.

2.8 Rationale for Evaluation of Hypersensitivity

Expansion of the use of platinum and taxane compounds for the treatment of recurrent disease has ushered in an increasing awareness of problematic drug-specific hypersensitivity reactions (HSRs).[44-48] The syndrome is manifested by flushing, dyspnea/bronchospasm, back pain, chest discomfort, pruritus, erythema, nausea, hypotension and occasionally bradycardia/tachycardia. They are profound experiences for patients. Although reported as early as the 1970's for platinum and the 1980's for paclitaxel, prophylaxis has been unable to completely eradicate these reactions often

considered by investigators as severe enough to warrant agent discontinuation. Markman, reporting on 205 patients treated with carboplatin, documented 24 (12%) with HSR occurring after a median of 8 courses. He noted that without prophylaxis, only 1 of 3 patients retreated with the agent were able to undergo infusion.[49] Recently, however, several investigators have reported in small single institution studies the success of retreatment programs for those patients suffering hypersensitivity reactions to either or both carboplatin and paclitaxel. These regimens, which include slower infusion, prolonged and repeated premedication prophylaxis and accelerated dosing over time, have been largely successful. Brown and colleagues reported on 32 patients demonstrating hypersensitivity reactions while undergoing treatment for gynecological malignancies. Twenty-three patients had recurrent ovarian or peritoneal cancer. Reactions to platinum (cisplatin and carboplatin) and paclitaxel were observed. Seventeen patients underwent a desensitization protocol and had re-treatment attempted. Seven out of 8 platinum HSRs and 8 out of 10 paclitaxel HSRs were successfully re-treated following desensitization. Lee and colleagues also reported successful reinfusion of paclitaxel, carboplatin or both in 57 patients (255 courses) using a desensitization protocol. Twelve percent of patients had breakthrough symptoms described as of lower severity than the index event – these were also successfully controlled and enabled subsequent retreatment.[48]

The incidence of hypersensitivity is largely unknown particularly in this era of nearly universal paclitaxel and platinum re-treatment. Estimates range from 2-16% for paclitaxel and 5-20% for cisplatin and carboplatin with the latter being reported with increasing frequency. No prospective trials to date have evaluated this incidence in the recurrent setting. Information will be useful in developing strategies to predict or modify re-treatment to avoid these dramatic complications of infusion.

## 2.9 Rationale for Quality of Life Assessment

The quality of life (QOL) component of this trial has two foci: evaluating the effects of the cytoreductive surgery and assessing the impact of adding bevacizumab to second-line paclitaxel and carboplatin for second-line and maintenance therapy.

The primary QOL question with regard to the surgery randomization is whether cytoreductive surgery is associated with improved quality of life due to its anti-tumor effect. The evaluation of this question is critical because, although cytoreductive surgery has the potential to increase survival and improve QOL through reducing tumor burden, potential surgical complications and recovery from surgery may adversely affect QOL. Thus, secondary cytoreductive surgery may initially produce a decline in quality of life, while patients recover from surgery and complications, followed by an improvement in quality of life due to reduced tumor burden.

With regard to the chemotherapy, the principle QOL question is whether the addition of bevacizumab to second-line carboplatin and paclitaxel, followed by maintenance therapy with bevacizumab is associated with better quality of life than carboplatin and paclitaxel combination therapy. The addition of maintenance treatment may present additional toxicities such as fatigue, rash, and diarrhea.[50-52] These toxicities could affect a range of quality of life areas.

Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O; Appendix III) a 37-item questionnaire that measures physical,

functional, social, and emotional well-being, along with a subscale that measures concerns specific to women with ovarian cancer. The physical, functional, social, and emotional well-being subscales comprise the FACT-G (General), which is considered appropriate for use with patients with any form of cancer. Version 4 of the FACT-G is widely used and has undergone psychometric testing and demonstrates good reliability and validity consistent with previously published data on earlier versions. In a validation study of the FACT-O (FACT-G subscales plus ovarian-specific subscales), the total scale and subscales demonstrated very good to excellent internal consistency reliability (0.74-0.92) and test-retest reliability (0.72-0.88).[53] Validity of the FACT-O was demonstrated by correlation with other quality of life measures, and by its relationship to performance status, treatment status, and disease stage. The FACT-O, particularly the physical well-being, functional well-being, and ovarian subscales were sensitive to changes in performance status over a two-three month period. To assess the effects of bevacizumab-related side effects on QOL, questions from the FACIT measurement system have been added related to rash, concerns about appearance, diarrhea, fatigue, and appetite (labeled "Additional Concerns (TSE)" in Appendix III).

In order to evaluate the effect of surgery on quality of life, patients will complete the Physical Functioning Subscale of the Rand 36-Item Short Form Health Survey (Rand SF-36). The Physical Functioning (PF) Subscale is a 10-item subscale of the Rand SF-36 a global quality of life questionnaire, designed to assess quality of life of patients across all medical conditions [54-56].

The PF Subscale consists of items concerning activities of daily living: walking, climbing stairs, bathing, dressing, and performance of physical activities, with each item rated on a three-point scale of limitation of activity due to the patients' health, from "not limited" to "limited a lot." Internal consistency of the PF subscale is excellent, with an alpha co-efficient ranging from 0.89 to 0.92.[56] The PF subscale has been found to significantly correlate with other physical functioning measures (Sickness Impact Profile [SIP], r=.67-.78; shortened Arthritis Impact Measurement Scale (sAIMS, r=.60). Further evidence of validity was provided by the PF subscale distinguishing between patients with serious and mild medical conditions.[57] Furthermore, the PF subscale has been found to be responsive to changes in functioning after surgical procedures (thoracic surgery for treatment of non-small-cell lung cancer, abdominal aortic aneurysm repair, and total hip arthroplasty [58]), and sensitive to differences in quality of life between laparoscopic and open surgical procedures [59,60] and between epidural and patient-controlled analgesia after colonic surgery.[57] Norms have been developed for all subscales of the SF-36, by gender and age groups, based upon 2,474 respondents, as well as for patients with physical limitations.[58, 59]

Eight questions will be included to measure specific quality of life problems after surgery (labeled "Additional Concerns (S)" in Appendix III). These questions will address issues such as pain, fatigue, problems with the surgical incision, and ostomy appliances. Similar questions have been used in GOG-0152 (A Phase III Randomized Study of Cisplatin And Taxol® with Interval Secondary Cytoreduction versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III Epithelial Ovarian Carcinoma). Several of the questions were taken from questionnaires in the FACIT quality of life measurement system.[61] others were drafted to be similar in format to FACIT questions.

## 2.10 Background and Rationale for Translational Research

The translational research component of this protocol will focus on the molecular and biochemical phenotype of recurrent ovarian cancer. It is well known that the vast majority of patients with advanced ovarian cancer who respond to initial therapy will recur. However, these recurrent tumors remain essentially a molecular enigma because of their general unavailability for analysis. A brief review of the GOG Tissue Bank demonstrated that less than 5% of ovarian cancer specimens are from sources other than the primary tumor. Further, only 22 specimens of recurrent ovarian cancer with attached clinical data have been banked.

This protocol provides an extraordinary opportunity to study these tumors, characterize them on a molecular basis, compare them to the original primary tumor, and determine the basis for disease recurrence and altered drug sensitivities. In the past five years, over 600 manuscripts on expression profiling of cancers using microarray technology have been published, illustrating the recognized utility of this approach in exploring questions of tumor biology and clinical correlates. The principles of class prediction and class discovery as they apply to the molecular classification of human cancers were exemplified by Golub et al., who used oligonucleotide microarrays to monitor gene expression in acute leukemias as a test case.[62] Class prediction identified and validated a subset of informative genes whose expression was highly correlated with previously defined classes. Further, subsequent studies have utilized these approaches to provide proof of the "molecular profiling principle" as well as to gain novel insights into clinical cancer problems. Using a specialized, lymphoid cell-specific cDNA microarray, Alizadeh et al. performed expression profiling of diffuse large B-cell lymphomas and identified two molecularly distinct forms of this malignancy that correlated with overall survival.[63]

Further, recent work on the problem of drug resistance has detailed multiple potential biochemical mechanisms, which may be critical for the development of drug resistance in ovarian cancer. For instance the expression level of DNA repair enzymes and membrane transporters have been implicated in cisplatin resistance while microtubule mutations have been shown to affect paclitaxel sensitivity.[64, 65] These *in vitro* determined mechanisms require testing and validation on in vivo derived tumor specimens.

GOG-0213 patients undergoing secondary cytoreduction will be able to provide archival formalin-fixed and paraffin-embedded primary or metastatic tumor, a pre-op serum specimen, a pre-op plasma specimen, formalin-fixed recurrent tumor, frozen recurrent tumor, formalin-fixed normal tissue and/or frozen normal tissue to establish an enduring resource for defining the molecular and biochemical phenotype of recurrent ovarian cancer. The pre-op serum and plasma will be prepared from blood drawn prior to secondary cytoreductive surgery. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the tissue, serum and plasma specimens submitted for the GOG-0213 patients undergoing secondary cytoreduction will be reevaluated based on evolving data in the field.

2.11 Rationale for the inclusion of fallopian tube carcinoma (FTCA)

Primary carcinoma of the fallopian tube is among the rarest malignancies of the female genital tract accounting for approximately 3.3/1,000,000 women annually. Despite its rarity, the disease shares many features of ovarian and primary peritoneal cancer including, risk factors (age and nulliparity), genomic alterations (LOH 3q and 8q, 1q, 5p, 7q, 12p and 20q), genetic abnormalities (Her 2-neu, P53, and k-ras mutations), natural history (local followed peritoneal metastases), response to chemotherapy, and anticipated survival by stage.[66-68] The latter feature is modeled after primary ovarian cancer as well. Most strikingly though is the relationship between BRCA mutation and the attendant increased risk of fallopian tube cancer over baseline. A life-time risk increase of 120 fold over background has been reported for women who harbor BRCA mutation. In fact, women diagnosed with FTCA may be at greater risk for harboring a BRCA mutation than women diagnosed with ovarian cancer. As such, women undergoing risk-reducing bilateral salpingo-oophorectomy (RRBSO) are recommended to have as much of the fallopian tube resected as possible and undergo step-sectioning as is performed for the ovary.

Since there appears to be a common set of environmental and genetic risk factors for FTCA and ovarian cancer, it is not surprising that the clinical approach for these two neoplasms is similar including primary surgical resection and debulking or staging, adjuvant platinum- and taxane-based chemotherapy and surveillance protocols (including CA-125). Based on these features and the lack of consensus as to the precise diagnostic criteria separating primary entities of the ovary, fallopian tube and peritoneum it is appropriate to consider FTCA within this spectrum of disease.

2.12 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and peritoneal primary cancer population treated by participating institutions.

## 3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

### 3.1 Eligible Patients

3.11 Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or fallopian tube carcinoma, which is now recurrent.

3.12 Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

3.13 Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles) and a treatment-free interval without clinical evidence of progressive disease lasting at least 6 months. Front-line therapy may have included a biologic agent (i.e. bevacizumab) but an interval of at least six months must have elapsed after completion of therapy.

3.131 A complete response to front-line chemotherapy must include: negative physical exam, negative pelvic exam, normalization of CA125, if elevated at baseline and negative radiographic assessment of disease.

3.132 Front-line treatment may include maintenance therapy following complete clinical or pathological response. However, recurrent disease must not be identified earlier than 6 months following completion of all anti-cancer treatment.

3.133 Patients who have undergone reassessment laparotomy or laparoscopy following primary therapy are eligible for this study as long as they demonstrated a pathologic complete response based on the surgical assessment (i.e. all obtained specimens were histologically negative for disease).

3.14 Patients must have clinically evident measurable or non-measurable disease. For the purpose of this study, *measurable disease* is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be more than or equal to 20 mm when measured by conventional techniques, MRI or CT, or more than or equal to 10 mm when measured by spiral CT. *Non-measurable disease* is either **symptomatic** ascites or pleural effusion. Patients with clinically evident non-measurable disease must also have either:

3.141 CA-125 $\geq$ two times the ULN. Patients registered onto the study with serum CA-125 levels less than 100 U/ml must be confirmed a second time within a period of not more than 4 weeks. Patients with a level greater or equal to 100 U/ml may be entered without confirmatory measurement. The CA-125 assessment for eligibility must be done at least 4 weeks after paracentesis or other surgical procedures.

3.142 Histologic confirmation of recurrence is required in the absence of an elevated CA-125 and measurable disease.

3.15 Patients must have adequate:

3.151 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/$mm^3$, equivalent to Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) Grade1.

3.152 Platelets greater than or equal to 100,000/$mm^3$. (CTCAE Grade 0-1).

3.153 Renal function: Creatinine ≤ 1.5 mg/dL (133 < mol/l) or creatinine clearance ≥ 60 ml/min

3.154 Hepatic function:

3.1541 Total bilirubin ≤ 1.5 ULN (CTCAE Grade 1).

3.1542 SGOT/AST and Alkaline Phosphatase ≤ 2.5 times the upper limit of normal in the absence of liver metastasis. SGOT/AST and Alkaline Phosphatase <5.0 times ULN in the presence of liver metastasis.

3.155 Patients must have a urine protein-to-creatinine ratio (UPCR) < 1.0 mg/dL. The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hr urine collection. Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24-hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24 hour urine). Send the sample to the lab with a request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as: protein concentration (mg/dL) / creatinine concentration (mg/dL).

3.16 Patients who are not candidates for surgical cytoreduction are eligible for the chemotherapy randomization. Patients are not considered candidates for surgical cytoreduction if complete cytoreduction in the estimation of the investigator is impossible or a medical infirmity precludes exploration and debulking.

3.17 Patients must have met the pre-entry requirements specified in Section 7.0.

3.18 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.19 Patients must have a GOG Performance Status of 0, 1, or 2.

3.110 Patients must be at least 18 years old.

3.2 Ineligible Patients

3.21 Patients who have received more than one previous regimen of chemotherapy (maintenance is not considered a second regimen).

3.22 Patients receiving concurrent immunotherapy, or radiotherapy.

3.23 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

3.24 Patients with a prior histologic diagnosis of borderline, low malignant potential (grade 0) epithelial carcinoma that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian or peritoneal primary cancer are eligible provided that they meet the criteria listed in Section 3.12.

3.25 Patients who require parenteral hydration or nutrition and have evidence of partial bowel obstruction or perforation.

3.26 Patients who have received prior chemotherapy for any abdominal or pelvic tumor are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than five years prior to registration, and that the patient remains free of recurrent or metastatic disease.

3.27 Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: Stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

3.28 Patients with uncontrolled infection.

3.29 Patients with concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy.

3.30 Patients with ≥ grade 2 peripheral neuropathy

3.31 Patients with a history of allergic reactions to carboplatin and/or paclitaxel or chemically similar compounds. Patients with allergic (hypersensitivity) reactions to these chemotherapeutic agents are **NOT** excluded **IF** they were successfully retreated following a desensitization program or protocol.

3.32 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

3.33 Patients of childbearing potential, not practicing adequate contraception, patients who are pregnant or patients who are nursing are not eligible for this trial. To date, no fetal studies in animal or humans have been performed. The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for the formation of new blood vessels during development, and

antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. In addition, there are unknown immediate and long-term consequences of chemotherapy administration to these women. In addition, surgical exploration as mandated by randomization during pregnancy may cause imminent mortal consequences. Further, it is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Subjects will be apprised of the large potential risk to a developing fetus.

3.35 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.36 Patients with active bleeding or pathologic conditions that carry high risk of bleeding such as a known bleeding disorder, coagulopathy, or tumor involving major vessels.

3.37 Patients with a history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases or a history of stroke within 5 years of the first date of treatment on this study.

3.38 Patients with clinically significant cardiovascular disease. This includes:

3.381 Patients with significant cardiac conduction abnormalities, i.e. PR interval > 0.24 sec or 2nd or 3rd degree AV block.

3.382 Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg.

3.383 Myocardial infarction, cardiac arrhythmia or unstable angina < 6 months prior to registration.

3.384 New York Heart Association (NYHA) Grade II or greater congestive heart failure.

3.385 Serious cardiac arrhythmia requiring medication.

3.386 Grade II or greater peripheral vascular disease (exception: (<24 hrs) episodes of ischemia managed non-surgically and without permanent deficit).

3.387 History of CVA within six months.

3.39 Patients who have had a major surgical procedure, open biopsy, dental extractions or other dental surgery/procedure that results in an open wound, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course

of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.

3.401 Patients undergoing pre-treatment secondary cytoreduction will undergo therapy with bevacizumab on cycle #2 (See Section 5.234).

3.402 Patients undergoing pre-treatment surgery for purposes other than cytoreduction may also participate provided they meet eligibility in Section 3.1. Patients randomized to arms containing bevacizumab will require a minimum 28 days since that procedure in order to participate.

## 4.0 STUDY MODALITIES

### 4.1 Carboplatin (Paraplatin®, NSC # 241240)

4.11 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

4.12 Solution Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

| Vial Strength | Diluent Volume |
|---|---|
| 50 mg | 5 ml |
| 150 mg | 15 ml |
| 450 mg | 45 ml |

These dilutions all produce a carboplatin concentration of 10 mg/ml.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

4.13 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.14 Stability: When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

4.15 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.16 Administration: See Section 5.2.

4.17 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation
Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms
Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance
Hepatic: Abnormal liver function tests including bilirubin, SGOT, and alkaline phosphatase
Electrolyte Changes: Abnormally decreased serum electrolyte values reported for sodium, potassium, calcium, and magnesium.
Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.

Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.
Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic-uremic syndrome has been reported rarely. Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.2 Paclitaxel (Taxol®, NSC #673089)

4.21 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300 mg vials.

4.22 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 ml is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.23 Storage: The intact vials can be stored in a temperature range between 2-25 C (36-77°F).

4.24 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

4.25 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.26 Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. See section 5.2.

4.27 Adverse Effects: Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, injection-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

4.3 Bevacizumab (NSC #704865, IND #7921)

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

4.31 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

4.32 How Supplied: "Bevacizumab" is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 100mg (25mg/mL – 4mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

*The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin®. Investigational bevacizumab and commercially available Avastin® may be produced at separate facilities and some differences may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.*

4.33 Storage and Stability: Bevacizumab is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2° to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

4.34 Preparation: Vials contain no preservative and are intended for single use only. **The calculated dose should be placed in a sterile, empty IV bag and diluted with a sufficient amount of 0.9% Sodium Chloride for Injection to obtain a final volume of 100 mL.** Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab solution must be administered within 8 hours.

4.35 Administration: Bevacizumab is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

4.36 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC #704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for bevacizumab.

| Category (Body System) | Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term) | 'Agent Specific Adverse Event List' (ASAEL) |
|---|---|---|
| ALLERGY/IMMUNOLOGY | | |
| | Allergic reaction/hypersensitivity (including drug fever) | ***Allergic reaction/hypersensitivity (including drug fever)*** |
| | Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) | |
| BLOOD/BONE MARROW | | |
| | Leukocytes (total WBC) | |
| | Neutrophils/granulocytes (ANC/AGC) | |
| CARDIAC ARRHYTHMIA | | |
| | Supraventricular arrhythmia NOS | |
| | Ventricular fibrillation | |
| CARDIAC GENERAL | | |
| | Cardiac ischemia/infarction | ***Cardiac ischemia/infarction*** |
| | Cardiac troponin I (cTnI) | |
| | Hypertension | ***Hypertension*** |
| | Hypotension | |
| | Left ventricular diastolic dysfunction | |
| | Left ventricular systolic dysfunction | |
| CONSTITUTIONAL SYMPTOMS | | |
| | Fatigue (asthenia, lethargy, malaise) | |
| | Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x $10^9$/L) | ***Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x $10^9$/L)*** |
| | Rigors/chills | ***Rigors/chills*** |
| | Weight loss | |
| DERMATOLOGY/SKIN | | |
| | Pruritus/itching | |
| | Rash/desquamation | ***Rash/desquamation*** |
| | Ulceration | |
| | Urticaria (hives, welts, wheals) | ***Urticaria (hives, welts, wheals)*** |
| | Wound complication, non-infectious | |
| **Category (Body System)** | **Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)** | **'Agent Specific Adverse Event List' (ASAEL)** |
| GASTROINTESTINAL | | |
| | Anorexia | ***Anorexia*** |
| | Colitis | |
| | Constipation | ***Constipation*** |
| | Diarrhea | |
| | Fistula, GI - Select | |
| | Heartburn/dyspepsia | ***Heartburn/dyspepsia*** |
| | Leak (including anastomotic), GI: large bowel | |
| | Mucositis/stomatitis (functional/symptomatic) - Select | ***Mucositis/stomatitis (functional/symptomatic) - Select*** |
| | Nausea | ***Nausea*** |
| | Perforation, GI - Select | |
| | Vomiting | ***Vomiting*** |
| HEMORRHAGE/BLEEDING | | |
| | Hemorrhage GI - Select | ***Hemorrhage GI - Select*** |
| | Hemorrhage, CNS | ***Hemorrhage, CNS*** |

| | | |
|---|---|---|
| | Hemorrhage, GU: vagina | |
| | Hemorrhage, pulmonary/upper respiratory: lung | ***Hemorrhage, pulmonary/upper respiratory: lung*** |
| | Hemorrhage, pulmonary/upper respiratory: nose | ***Hemorrhage, pulmonary/upper respiratory: nose*** |
| | Hemorrhage/Bleeding - Other (varices-gastric/esophagus) | |
| INFECTION | | |
| | Infection with normal ANC or Grade 1 or 2 neutrophils - Select | ***Infection with normal ANC or Grade 1 or 2 neutrophils - Select*** |
| METABOLIC/LABORATORY | | |
| | Alkaline phosphatase | |
| | ALT, SGPT (serum glutamic pyruvic transaminase) | |
| | AST, SGOT (serum glutamic oxaloacetic transaminase) | |
| | Bilirubin (hyperbilirubinemia) | |
| | Creatinine | |
| | Proteinuria | ***Proteinuria*** |
| NEUROLOGY | | |
| | CNS cerebrovascular ischemia | ***CNS cerebrovascular ischemia*** |
| | Dizziness | |
| | Neurology – Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome (RPLS)) | |
| PAIN | | |
| | Pain - abdomen NOS | |
| | Pain - chest/thorax NOS | ***Pain - chest/thorax NOS*** |
| | Pain - head/headache | ***Pain - head/headache*** |
| | Pain - joint | ***Pain - joint*** |
| | Pain - muscle | |
| | Pain - NOS | |
| **Category (Body System)** | **Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)** | **'Agent Specific Adverse Event List' (ASAEL)** |
| PULMONARY/UPPER RESPIRATORY | | |
| | Bronchospasm, wheezing | |
| | Cough | ***Cough*** |
| | Dyspnea (shortness of breath) | |
| | Nasal cavity/paranasal sinus reactions | |
| | Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis) | ***Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)*** |
| RENAL/GENITOURINARY | | |
| | Renal/Genitourinary - Other (nephrotic syndrome) | |
| SYNDROMES | | |
| | Cytokine release syndrome/acute infusion reaction | ***Cytokine release syndrome/acute infusion reaction*** |
| VASCULAR | | |
| | Thrombosis/thrombus/embolism | ***Thrombosis/thrombus/embolism*** |
| | Visceral arterial ischemia (non-myocardial) | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Also reported on bevacizumab trials but with the relationship to bevacizumab still undetermined:**
Blood/bone marrow - Hemoglobin; idiopathic thrombocytopenia purpura; platelets
Cardiac general - Cardiac arrest; pericardial effusion
Coagulation - DIC
Death - Sudden death (cause unknown)
Dermatology/skin - Hypopigmentation
Gastrointestinal- Rectal abscess/necrosis; small bowel obstruction; taste alteration
Metabolic/laboratory - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
Musculoskeletal/soft tissue - Aseptic necrotic bone; gait/walking; myasthenia gravis
Neurology - Aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope
Ocular/visual - Cataract; watery eye
Pulmonary/upper respiratory - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
Renal/genitourinary - Urinary frequency

**Note**: Bevacizumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

**(For a more complete listing of reported AEs, please refer to the Investigator's Brochure)**

**4.37** General Information on Adverse Effects of Bevacizumab

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE v3.0 terms is included above. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice.

Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.[97] In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[98] In patients $\geq$ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with

gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL $\pm$ bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencepalopathy Syndrome (RPLS), or similar leukoencepalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical finding are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter. In RPLS associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. RPLS/ PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is the key to diagnosis. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage.

Neutropenia: when combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevaciumab arm + IFL vs 14% in the IFL arm (grade 4 neutropenia was 3% vs 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutorpenia (27% vs 17%), febrile neutropenia (5.4% vs 1.8%), and an increased risk of infection with neutropenia (4.4% vs 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs none in the chemotherapy control arm.

4.38 Clinical Supplies: Bevacizumab (NSC 704865) will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Bevacizumab will be supplied in 4 mL fill glass vials each containing 100 mg (bevacizumab) of bevacizumab.

4.39 Ordering Supplies of Bevacizumab: See Section 4.5.

## 4.4 Ordering Supplies of Bevacizumab

4.41 Initial supplies of bevacizumab will be sent to the registering investigator, when appropriate, automatically following randomization. This randomization will be performed by the GOG Statistical and Data Center in Buffalo, NY. The assigned patient ID number must be recorded by the registering institution for proper vial dispersion. Once a patient has been registered with the GOG Statistical and Data

Center, the GOG Statistical and Data Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG Statistical and Data Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, GOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday. The initial request will be for **XX** vials (minimum of 2 courses / 2 cycles / 6 week supply). Three weeks after the initial electronic request (i.e., three weeks before needed), sites may reorder an additional 3 courses / 3 cycles / 9 week supply by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The assigned patient ID number (e.g., "999-0213-001"), the patient initials (e.g., "FML"), the number of vials remaining from the initial shipment, and the patient's weight (in KG) should be entered on each order. All drug orders will be shipped directly to the physician registering the patient.

4.42 Drug Transfers: Vials **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0213-001") and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "**GOG-0213**").

4.43 Drug Returns: Only unreconstituted drug supplies should be returned to the PMB. The investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0213-001") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field.

4.44 Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999-0213-001") on this protocol.

**GOG-0213 Shipment Schedule**

| Patient Randomized with GOG | Initial e-Order Transmitted by GOG | Initial e-Order Received and Approved by PMB | Initial Order Shipped By PMB | Initia Receive |
|---|---|---|---|---|
| Monday | Monday | Tuesday | Wednesday | Thu |
| Tuesday | Tuesday | Wednesday | Thursday | Fr |
| Wednesday | Wednesday | Thursday | Monday | Tu |
| Thursday | Thursday | Friday | Monday | Tu |
| Friday | Friday | Monday | Tuesday | Wed |

**arrival time approximate / shipments sent by Federal Express**

4.5 Docetaxel (Taxotere® RP-56976, NSC #628503)

4.6 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

4.45 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

4.46 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.

4.47 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

4.48 Adverse Effects: Consult the package insert for the most current and complete information.

4.49 Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

## 5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient entries will be accepted, an official signed CTSU IRB Certification Form and a CTSU IRB/Regulatory Approval Transmittal Sheet (forms can be downloaded at **www.ctsu.org**) must be received by the CTSU Regulatory Office. These forms can be faxed or mailed to:

**CTSU Regulatory Office**
**Coalition of National Cancer Cooperative Groups**
**1818 Market Street, Suite 1100**
**Philadelphia, PA 19103**
**1-888-823-5923**
**FAX 215-569-0206**

### 5.1 Patient Entry and Registration

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

5.11 An approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

5.12 All eligibility requirements indicated in Section 3.0 must be satisfied.

5.13 The Fast Fact Sheet data must be gathered.

5.14 Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page. Assistance is available from the Statistical and Data center by phone if necessary (800-523-2917).

5.141 In order to obtain investigational drug from the Pharmaceutical Management Branch (PMB), the treating physician must have an active NCI Investigator Number. If the treating physician's investigator number is not active, the drug order will **not** be processed. To obtain or renew an NCI Investigator Number, please visit the CTEP's Investigator Registration page at http://ctep.info.nih.gov/resources/investigator2.html.

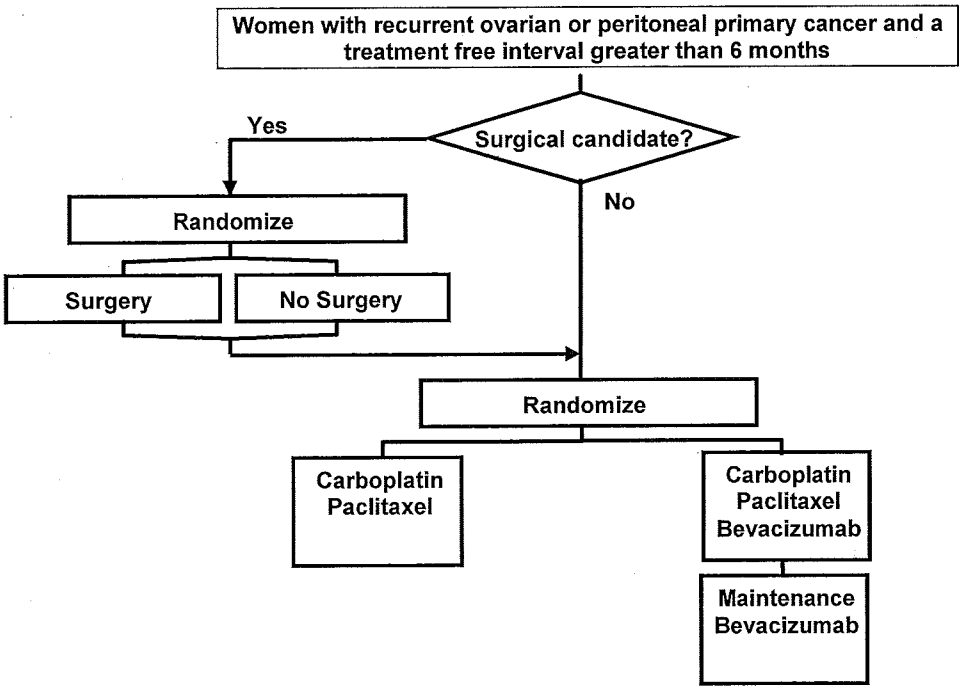
5.15 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan

5.21 Patients meeting eligibility requirements will be considered first for the surgical randomization aspect of the trial. Suitability for secondary cytoreduction will be made by the individual patient's Attending Physician. Guidelines for consideration in assessing candidacy for secondary cytoreduction are listed in Section 5.211. If the patient is considered to be a suitable surgical candidate she will undergo randomization as outlined in Section 5.22. If she is considered not to be a suitable surgical candidate she will be allowed to participate in the chemotherapy randomization aspect of the trial as outlined in Section 5.23. Patients undergoing surgical randomization will also be randomized to a chemotherapy regimen at the same time.

5.211 Guidelines for Secondary Cytoreduction: The goal of secondary cytoreduction is **COMPLETE REMOVAL OF ALL VISIBLE DISEASE**. While no specific eligibility can be globally provided, patients with recurrent disease which will not be addressed at surgery should not undergo surgical randomization. In general, women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction. Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc) are poor candidates, if the disease is felt unresectable by preoperative evaluation. Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT). Although it is recognized that patients with longer treatment-free intervals may be considered better surgical candidates (providing some expansion of the preoperative tumor volume characteristics) than those with shorter treatment-free intervals, the primary tenet of surgery for this study in all women enrolled in this arm is complete surgical resection (no visible residual).

5.22 Randomization I: ***Surgery***: Patients entered onto the surgical arm of the trial will undergo abdominal exploration with cytoreduction as outlined in (Appendix IV) within 4 weeks of registration. Chemotherapy will be administered following recovery up to 6 weeks after surgery.




5.23 Randomization II: ***Chemotherapy***

5.231 Regimens:

| Arm | Regimen* | Schedule | Maintenance Regimen |
|---|---|---|---|
| **I** | Paclitaxel 175 mg/m$^2$ **<br>Carboplatin AUC 5 | Every 21 days<br>(Section 5.24) | None |
| **II** | Paclitaxel 175 mg/m$^2$ **<br>Carboplatin AUC 5<br>Bevacizumab 15 mg/kg | Every 21 days<br>(Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |

*All chemotherapy doses on day one unless otherwise indicated. For those patients randomized to cytoreductive surgery, bevacizumab is to be started at the 2$^{nd}$ cycle of therapy.
** Note: docetaxel 75mg/m$^2$ IV over 1 hour may be substituted for paclitaxel (see Sections 5.233 and 6.161).

5.232 Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

5.233 Sequence and timing of drug administration:

- **Paclitaxel** will be infused over 3 hours. (Note, for circumstances in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m$^2$ see Sections 6.161 and 6.167).
- **Carboplatin** will be administered as a 30-minute infusion. When administered in conjunction with other medications, carboplatin will be infused after the other agents. Carboplatin, either alone or in combination should be premedicated with dexamethasone (either IV

or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

- **Bevacizumab** administration will be as a continuous intravenous infusion following paclitaxel infusion. Anaphylaxis precautions should be observed during bevacizumab administration. The initial dose would be administered over 90 ± 15 minutes. If no adverse reactions (including fever and or chill) occur, the second dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.
  - **Bevacizumab has been associated with an increase in wound complications and bowel perforations in post-operative patients. Thus, patients in Randomization I who undergo surgery and are to receive bevacizumab after Randomization II will have the first cycle of therapy without bevacizumab. They will receive it in cycle #2.**

5.234 Pre-Medication:

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

When carboplatin and paclitaxel are administered with bevacizumab, it is recommended that the preparatory regimen as outlined above should be given 60 minutes before infusion to reduce the risk of hypersensitivity associated with these agents.

In the event of a prior bevacizumab hypersensitivity reaction the prophylactic regimen should be repeated prior to subsequent doses of bevacizumab (Section 5.2551). Thus, the patient will be premedicated prior to paclitaxel AND prior to bevacizumab.

For all courses where docetaxel is to be administered, (see Sections 6.161 and 6.167) it is recommended that patients be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate $H_1$ blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

5.235 Antiemetic Regimens

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,
- Granisetron 10 mcg/kg IV (or 2 mg PO) 30 minutes prior to chemotherapy, with or without lorazepam 0.5 – 2.0 mg IV 30 minutes prior to chemotherapy.

5.236 Dosing of Carboplatin

The dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Jelliffe formula.

- Initial dose of carboplatin must be calculated using GFR. In the absence of new renal obstruction or other renal toxicity greater than or equal to CTC grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted. See section 6.153 for details of significant variances in renal function.
- In patients with an abnormally low serum creatinine (less than or equal to 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.6 mg/dl. If a more appropriate baseline creatinine value is available within 4 weeks of treatment that may also be used for the initial estimation of GFR.
- Calvert Formula: Carboplatin dose (mg) = target AUC × (GFR + 25)
- For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance. The creatinine clearance (Ccr) is estimated by the method of Jelliffe using the following formula:

$$Ccr = 0.9 \times \frac{\{98 - [0.8\ (age - 20)]\}}{Scr}$$

Where: Ccr = estimated creatinine clearance in ml/min
Age = patient's age in years (from 20-80)
Scr = serum creatinine in mg/dl

5.24 Duration of treatment – Arm I:

5.241 Patients with measurable disease achieving clinical complete response (negative physical exam, negative CT scan or MRI and normal CA-125) (CR; Section 8.131) during the chemotherapy phase will be treated with a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles), whichever is greater.

5.242 If stable or partial regression is the maximum documented response, patients will continue their chemotherapy to a maximum of 6 cycles (see Section 8.14) or adverse effects (see Section 6.0). Patients will then be

followed off therapy until documented progression occurs. (See Section 8.14)

5.243 If progressive disease is observed while on therapy, patients will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.244 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue therapy for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable lesions) will have chemotherapy stopped after six cycles. .

5.25 Duration of treatment – Arm II:

5.251 Patients with measurable disease achieving clinical complete response (CR; Section 8.131) during the chemotherapy phase will be treated for a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles) and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.

5.252 If stable or partial regression is the maximum documented response, patients will receive 6 cycles of therapy and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.

5.253 If progressive disease is observed while on therapy, patients in all arms will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.254 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue chemotherapy and the biologic agent for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable disease) will have chemotherapy stopped after six cycles. The maintenance regimen will begin after completing chemotherapy and continue until progression or adverse effects preclude additional treatment.

5.255 Dosing of bevacizumab

Bevacizumab will be administered at 15 mg/kg IV. Patient weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. For patients undergoing the second surgical procedure baseline weight for calculating the bevacizumab dose should be post-op. If a patient's weight changes by $\geq$ 10% during the course of

the study, the bevacizumab dose will be recalculated.

5.2551 Supportive Care Guidelines for Bevacizumab

If an infusion-related adverse reaction occurs, the patient should be pre-medicated prior to subsequent doses of bevacizumab (Section 5.234); however, the infusion time for bevacizumab may not be decreased for the next infusion. If a patient experiences an infusion-associated averse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes ± 15 minutes

.

5.26 Biometric considerations in dose calculation

Maximum body surface area used for dose calculations will be 2.0 $m^2$ as per GOG Chemotherapy Procedures Manual

5.3 Secondary Cytoreduction:

The value of secondary surgical cytoreduction is being evaluated in this trial through a randomization of surgical candidates deemed appropriate by their treating physicians. Participation in the surgical randomization arm of this trial is **NOT** required for entry on this study. Patients with recurrent disease, meeting entry criteria but deemed not appropriate for surgical exploration are eligible to participate in the chemotherapy randomization. Those patients for whom their treating physicians consider appropriate for surgery will be randomized to either secondary cytoreduction or no surgery prior to a second randomization of chemotherapy. Surgical exploration should be undertaken within 28 days of registration onto this study.

5.31 Procedures and goals of secondary cytoreduction are outlined in Appendix IV.

5.32 Please see Section 7.2 for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix V for a detailed description of the Specimen Procedures for GOG-0213.

## 6.0 TREATMENT MODIFICATIONS

### 6.1 Dose Modifications:

Since chemotherapy in the recurrent setting is largely palliative, infusion without routine use of growth factor support will be attempted. Certain chemotherapy combinations have additive hematologic toxicity and other combinations are characterized by differing hematologic toxicity. Therefore, dose modification will be based on dose-limiting toxicity (DLT) for either or both neutropenia (ANC) or thrombocytopenia (PLT) and conducted as outlined in the following table below.

6.11 Dose-limiting neutropenia (DLT-ANC) is defined as:

- Febrile neutropenia: febrile is defined as fever ≥ 38.5°C, with or without documented infection in the presence of an ANC of 1000 cells/$mm^3$ or less
- Prolonged Grade IV ANC persisting ≥ 7 days.
- Uncomplicated Grade IV ANC, < 7 days, is NOT a DLT.

6.12 Dose-limiting thrombocytopenia (DLT-PLT) is defined as:

- Grade IV thrombocytopenia (< 25,000/$mm^3$)
- Grade III thrombocytopenia (25,000 to 50,000/ $mm^3$) complicated by bleeding, easy bruising, petechiae or requiring platelet transfusion (see Section 6.141)
- Uncomplicated Grade III thrombocytopenia is NOT a DLT

6.13 Guidelines for dose modification based on dose-limiting neutropenia and thrombocytopenia: (nadirs)

**Table A**

| DLT ANC‡ | DLT PLT§ | First Occurrence | Second Occurrence | Third Occurrence |
|---|---|---|---|---|
| Yes | No | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Add myeloid growth factor **AND** maintain all drug doses | Off Study Treatment, Follow-up Continued |
| Yes | Yes | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Off Study Treatment, Follow-up Continued | |
| No | Yes | Decrease one AUC unit **AND** maintain other drug doses * | Off Study Treatment, Follow-up Continued | |

‡ DLT-ANC: Neutropenic Dose-Limiting Toxicity (Section 6.11)

§ DLT-PLT: Thrombocytopenic Dose-Limiting Toxicity (Section 6.12)

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167, dose modifications can be found in Table B-2.

6.14 Adjustments for Hematologic Toxicity

6.141 **Hemorrhage**: Patients receiving bevacizumab who develop a CTCAE V3.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V3.0 Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met:

- bleeding has resolved
- blood hemoglobin level is stable (serial measures with less than 10% change)
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence.

Patients who experience delay of resolution according to the above criteria for greater than 3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE V3.0 Grade 4 hemorrhage will be taken off study treatment.

6.142 **Thrombosis:**

Arterial Thrombosis
Patients will be taken off study treatment for ≥ CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

Venous Thrombosis
Treatment will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. If the planned duration of full-dose anticoagulation is ≤ 3 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 3 weeks, treatment may be resumed during the period of full dose anticoagulation if ALL of the following criteria are met (otherwise the patient will be taken off study treatment):

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.
- The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The subject must not have had hemorrhagic events while on study.
- The patient is benefiting from treatment (no evidence of disease progression).

Patients with symptomatic CTCAE Grade 4, or recurrent/worsening thromboembolic events after resumption of bevacizumab, will be taken off study treatment.

6.143 **Coagulopathy**: For CTCAE V3.0 Grade 3 or 4 coagulopathy: hold treatment, until PT resolves to Grade 1. For patients with PT/INR > therapeutic range while on therapeutic warfarin, hold treatment until PT/INR within therapeutic range. Patients experiencing treatment delay >3 weeks because of failure to meet the above criteria will be taken off study.

**Table B-1 Regimen modifications for DLT's (6.11-613), hematologic toxicities (6.141-6.143) and delayed hematologic toxicity (6.153)**

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I | Paclitaxel *<br>Carboplatin | 135 mg/m$^2$<br>AUC 4 | 175 mg/m$^2$<br>AUC 5 |
| II | Paclitaxel *<br>Carboplatin<br>Bevacizumab | 135 mg/m$^2$<br>AUC 4<br>15 mg/kg | 175 mg/m$^2$<br>AUC 5<br>15 mg/kg |

* See Table B-2 below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

**Table B-2 Dose Levels for Docetaxel***

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I | Docetaxel | 65 mg/m$^2$ | 75 mg/m$^2$ |
| II | Docetaxel | 65 mg/m$^2$ | 75 mg/m$^2$ |
| III | Docetaxel | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.15 General Guidelines for **Delayed Hematologic Toxicity**

6.151 No subsequent cycle shall begin until the absolute neutrophil count (ANC) ≥ 1,500/mcl and platelets ≥ 100,000/mcl.

6.152 Failure of the counts to recover appropriately by day 21 will require delay of the subsequent treatment until adequate count recovery.

6.153 Patients who require a delay of greater than 1 but less than 2 weeks for adequate count recovery (with or without growth factors) will have subsequent treatment with a one level dose reduction. Patients who require a delay of greater than 2 weeks or who have a second delay of greater than 7 days will require the use of myeloid growth factors in all subsequent cycles.

6.154 Patients who require a delay of greater than 3 weeks for adequate count recovery (with or without growth factors) will be removed from study treatment, but follow-up will continue.

6.155 There will be no dose modification on the basis of uncomplicated WBC or ANC nadirs.

6.156 Patients will NOT receive prophylactic thrombopoietic agents on this study.

6.1561 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

6.1562 Patients may not receive amifostine or other protective reagents, unless indicated in the study design.

6.16 Adjustments for Non-hematologic Toxicity

Individual agents may be associated with specific non-hematological toxicity which warrants dose modification. Allowable dosing modifications are presented in the following table:

**Table C Regimen modifications for non-hematologic toxicities (see dose adjustments per toxicity type as outlined below**

| Agent | -2 Level | -1 Level | Starting Dose Level |
|---|---|---|---|
| Carboplatin | Off study treatment | AUC 4 | AUC 5 |
| Paclitaxel | 110 mg/m$^2$ | 135 mg/m$^2$ | 175 mg/m$^2$ |
| Bevacizumab | Off study treatment | 15 mg/kg | 15 mg/kg |
| Docetaxel * | 55 mg/m$^2$ | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.161 **Neurologic toxicity:** Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due then paclitaxel should be withheld from all subsequent chemotherapy cycles and docetaxel substituted for paclitaxel unless medically contraindicated, according to Section 5.233. If peripheral neuropathy fails to recover to Grade $\leq 2$ by a maximum delay of three weeks from time therapy is due, then the patient is removed from study.

In such cases where docetaxel has been substituted for paclitaxel, if CTCAE Grade 3 or 4 peripheral neuropathy occurs during or after the first cycle of docetaxel substitution then subsequent doses of docetaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade $\leq 2$. If peripheral neuropathy fails to recover to Grade $\leq 2$ by a maximum delay of three weeks from time therapy is due, then the patient is removed from study.

6.162 **Gastrointestinal toxicity:**

There will be no dose modifications for nausea, diarrhea, or constipation. It is recommended that routine medical measures be employed to manage nausea and constipation.

6.163 **Renal toxicity:** If renal function worsens on therapy, an investigation for underlying causes should be undertaken. Calculated or measured creatinine clearance under 40 ml/min or significant worsening of the renal function (50% reduction in calculated CrCl) requires withholding treatment until a cause is identified or renal function improves. In particular, disease progression should be ruled out. In these patients creatinine clearance should be evaluated weekly. If calculated or measured CrCl is less than 40 ml/min after a two-week delay, the Study Chair must be notified. No treatment is to be given to a patient with a calculated or measured CrCl less than 40 ml/min.

6.164 **Proteinuria:** Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.

UPC ratio < 3.5 Continue bevacizumab.
UPC ratio > 3.5 hold bevacizumab until UPC ratio recovers to <3.5. If bevacizumab is held for > 3 weeks, the patient is removed from study.
Grade 4 or nephrotic syndrome: Patient is removed from study.

6.165 **Hepatic toxicity:** Hepatic toxicity is not expected as a direct complication of chemotherapy in this population using the prescribed dose and schedule for each regimen. However, the development of grade 3 (or greater) elevations in SGOT (AST), alkaline phosphatase or bilirubin requires reduction of one dose level in all study drugs with the exception of carboplatin and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If therapy is held for > 3 weeks the patient is removed from study.

6.166 There will be no dose modifications for alopecia.

6.167 **Hypersensitivity reaction to paclitaxel or bevacizumab:** The occurrence of a hypersensitivity reaction to paclitaxel or bevacizumab is **not** considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication (such as decadron 20 mg IV and diphenhydramine 50 mg IV 30 minutes prior to reinfusion) to prevent hypersensitivity reaction and may utilize a slow initial infusion rate of the suspected agent which is gradually increased to the standard infusion rate in the absence of reaction (such as 1 cc of the original IV solution diluted in 100 ml over 10 minutes, then 5 cc in 100 ml over 10 minutes then 10 cc in 100 ml over 10 minutes and finally, the original solution at the original speed). However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic

or infusional reactions to bevacizumab, the patient is removed from study. In the event of recurrent hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel, according to guidelines in Sections 5.233 and 6.161.

**Hypersensitivity reaction to carboplatin**: The occurrence of a hypersensitivity reaction to carboplatin may occur in this previously treated population. Successful retreatment has been reported with a modified dilution and infusion schedule.[74, 75] A suggested desensitization protocol that may be used in patients with a carboplatin hypersensitivity is reduced infusion dose of 1:1000 dilution (0.1cc in 100 ml) over 1 hour, followed by a 1:100 dilution (1.0 cc in 100 ml) over 1 hour, followed by a 1:10 dilution (10 cc in 100 ml) over 1 hour, followed by 1:1 concentration for the remaining infusion. Patients experiencing a significant hypersensitivity reaction to carboplatin may be removed at the discretion of the treating physician if it is felt to be unsafe to offer a desensitization program.

6.168 **Hypertension**: Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab included ACE inhibitors, Beta blockers, diuretics, and calcium channel blockers.

- For controlled hypertension, defined as systolic $\leq$ 150 mm Hg and diastolic $\leq$ 90 mmHg, continue therapy;
- For uncontrolled hypertension (systolic > 150 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE V3.0 Grade 4, hold treatment for one week with anti-hypertensive therapy initiated or continued.
- If hypertension is controlled and symptomatic hypertension has resolved by three weeks after holding treatment, continue all therapy.
- If hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE V3.0 Grade 4, persists after three weeks after holding treatment, the patient is removed from study.
- Any patient developing CTCAE V3.0 Grade 4 hypertension will be removed from study.

6.169 **Wound disruption**: Patients will be removed from study in the event of a wound disruption requiring medical or surgical intervention.

6.1610 **Bowel perforation/obstruction/fistula/GI leak**: For new development of bowel perforation, bowel obstruction (partial or complete), fistula, or GI leak (any grade); the patient will be taken off study treatment.

6.1611 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs.

6.1612 **Weight loss:** If a patient's weight changes by ≥ 10% during the course of the study, the doses of carboplatin and bevacizumab will be recalculated. For patients undergoing the second surgical procedure the baseline weight for calculating the carboplatin and bevacizumab should be the patient's postoperative weight.

6.1613 **RPLS (Reversible Posterior Leukoencephalopathy Syndrome) or PRES (Posterior Reversible Encephalopathy Syndrome):** Hold bevacizumab in patients with symptoms/ signs suggestion of RPLS/ PRES; subsequent management should include MRI scans and control of HTN. Discontinue bevacizumab upon diagnosis of RPLS/ PRES

6.17 No dose-escalations are allowed on this study.

## 7.0 STUDY PARAMETERS

### 7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s). Specimen requirements for research are provided in Section 7.2

| | Pre-Treatment | | During Chemotherapy Phase | | | During Maintenance/Surveillance Phase | | |
|---|---|---|---|---|---|---|---|---|
| Observations and Tests | Prior to Surgery | Prior to chemo-therapy | Weekly | Prior to Each Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Prior to Every Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Q 3 Months x 8 then q 6 Months |
| History & Physical | 1 | 1 | | X | | | X | |
| Blood pressure | 1 | 1 | 2 | X | | X | X | |
| Toxicity Assessment | | | | X | | | X | |
| CBC/Differential/ Platelets | 3 | 3 | X | 4 | | | 4 | |
| Urine Protein-Creatinine Ratio (UPCR) | 3,5 | 3, 5 | | | 6 | | 6 | |
| Serum Creatinine | 3 | 3 | | 4 | | | 4 | |
| Bilirubin, SGOT/AST, Alkaline Phosphatase | 3 | 3 | | 4 | | | 4 | |
| Ca/PO4/Mg | | 3 | | 7 | | | 7 | |
| Serum CA-125 Level | 1 | 1 | | 4,13 | | | 4,13 | |
| PT/PT INR/PTT | 3 | 3 | | 8 | | | 8 | |
| Audiogram | | 9 | | | | | | |
| EKG | 1 | 1 | | | | | | |
| Radiographic Tumor Measurement | 1,10 | 1, 10 | | | 11 | | | 11 |
| Chest X-Ray | 1,12 | 1, 12 | | | | | | |
| QOL Survey | X,14 | X, 14 | | | 14 | | 14 | 14 |
| Incision Check | | X | 15 | | | | | |

1. Must be obtained within 28 days of first treatment. For those patients randomized to cytoreductive surgery, these observations are repeated prior to initiating chemotherapy.
2. Blood pressure should be assessed at least weekly during the first cycle of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion.
3. Must be obtained within 14 days prior to initiating chemotherapy.
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Urine protein should be assessed by UPCR (see Section 3.37 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
6. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab:
7. When clinically indicated
8. For patients on prophylactic or therapeutic anticoagulation, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin.
9. For patients with a history of hearing loss; repeat as clinically indicated
10. An initial CT scan (with intravenous and oral contrast, unless contraindicated) or MRI (with gadolinium, unless contraindicated and fat suppression sequence) of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within 4 weeks of registration and beginning treatment. PET-CT imaging alone cannot be used to establish extent of post-operative disease residuum unless also performed with CT or MRI as described.
11. Follow-Up Radiographic Assessment of Disease (in patients with measurable and non-measurable disease). Imaging should use the same modality and encompass the same fields as in the initial pre-treatment evaluation should be repeated with the following schedule:
    a) Within 28 days of first treatment.
    b) If the patient was randomized to cytoreductive surgery, then repeat radiographic assessment within 14 days of initiating chemotherapy.
    c) After cycle 3 (before cycle 4) of paclitaxel-carboplatin
    d) After cycle 6 of paclitaxel-carboplatin.
    e) Every three months after completion of chemotherapy during the maintenance/surveillance phase.
    Imaging assessments as part of this protocol can be discontinued if disease progression is confirmed according to guidelines in section 8.3. However, if disease progression is based only on rising CA-125 criteria, then radiographic imaging must be obtained within two weeks following the date CA-125 based progression was documented.
12. Not required if CT or MRI of chest already performed at pre-treatment baseline.
13. Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule.
14. See Section 7.3. QOL surveys are to be assessed for at most 6 time points:
    a) prior to surgery (for those randomized to cytoreductive surgery).
    b) prior to initiating chemotherapy.
    c) prior to cycle 3 (6 weeks after starting chemotherapy).
    d) prior to cycle 6 (15 weeks after staring chemotherapy).
    e) 6 months after starting chemotherapy.
    f) 12 months after starting chemotherapy.
15. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection may initiate therapy, but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.1512 and Adverse Events reporting in Section 10.3.

## 7.2 Translational Research For Patients Randomized To Surgery

### 7.21 Specimen Requirements

A total of seven specimens will be sought from each GOG-0213 patient randomized to have secondary cytoreductive surgery. Three of these will be MANDATORY and four will be HIGH-PRIORITY OPTIONAL. Please see below for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix V for a detailed description of the Specimen Procedures for GOG-0213. A copy of Form SP will need to be completed online and submitted to the GOG Statistical and Data Center (SDC) as specified in Section 10.3.

**Quick Scan Summary of the Specimen Requirements for GOG-0213.**

***(See Appendix V for detailed instructions for collecting, processing, storing, packing and shipping specimens for GOG-0213.)***

| **Required Specimens (Specimen Codes)**[1] *only for patients randomized to have secondary cytoreductive surgery* | **Form SP Label in Forms Tracking System**[2] | **Collection Time Points and Requirements** *for patients who are enrolled at GOG or CTSU Institutions, are randomized to have secondary cytoreductive surgery and give permission for their tissue, serum and/or plasma to be used for this research study* | **Deadlines and Recommendations** [2] |
|---|---|---|---|
| Archival Formalin-Fixed and Paraffin-Embedded Primary or Metastatic Tumor (FT01) either<br>• 1st choice: Block<br>• 2nd choice: 16 Unstained Slides | SP-FT01-0213 | Archival primary or metastatic tumor must have been collected prior to initiating primary chemotherapy.<br><br>**Mandatory** requirement. | Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. FT01 could also be included in the dual chamber kit if available when the other specimens were ready to ship to the Bank.<br><br>Submit Form SP for FT01 to the SDC online within 8 weeks of study entry. |
| Pre-Op Serum (SB01)<br><br>Pre-Op Plasma (PB01) | SP-SB01-0213<br><br>SP-PB01-0213 | After providing consent for this research study but prior to undergoing secondary cytoreductive surgery.<br><br>**Optional but high priority** requirement. | Ship the FR01 and RR01 (mandatory requirement) and any of the optional specimens (SB01, PB01, FN01 and/or RN01) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible as described in Appendix V.<br><br>Submit Form SP for each of these specimens to the SDC online within 7 days of surgery. |
| Formalin-Fixed Recurrent (FR01) | SP-FR01-0213 | During secondary cytoreductive surgery.<br><br>**Mandatory** requirement. | |
| Frozen Recurrent (RR01) | SP-RR01-0213 | | |
| Formalin-Fixed Normal Tissue[3,4] (FN01) | SP-FN01-0213 | During secondary cytoreductive surgery.<br><br>**Optional but high priority** requirement. | |
| Frozen Normal Tissue[3,4] (RN01) | SP-RN01-0213 | | |

[1] Label each specimen with the protocol number (GOG-0213), a GOG Bank ID (# # # # - # # – G # # #), a specimen code (see above) and the collection date (mm/dd/yyyy).

[2] Form SP must be submitted to the SDC online as specified in Section 10.3 for each patient randomized to undergo secondary cytoreductive surgery regardless of whether or not the specimens will be submitted for research. Research specimens must be shipped to the GOG Tissue Bank in Columbus Ohio with copies of the SP Forms as specified in Appendix V.

[3] **Quantity of tissue needed for research: Please submit as much tissue as possible for research. Gram quantities are ideal. There is a minimum requirement of 500 mg or 0.5 $cm^3$ (slightly larger than a pencil eraser).** Larger amounts of tissue will allow for replicate laboratory testing to be performed and will enable multiple assays to be run on the same specimen.

[4] **Normal tissue can be any normal epithelial tissue including non-involved ovary, fallopian tube, uterus, cervix, or skin. When normal epithelium is not available, please submit non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.** Please try to submit normal epithelium whenever possible as this type of tissue will serve as the most appropriate control for the laboratory testing to be preformed for this protocol. **Note for the pathologist,** in the unlikely event that any tumor tissue is subsequently identified within the normal tissue submitted for research, the Pathology Department at the treating institution will be informed and the material will be immediately returned for diagnostic purposes.

## 7.211 Tissue Specimens

### 7.2111 Metastatic Tumor Tissue for Research

**Archival formalin-fixed and paraffin embedded metastatic tumor tissue (FT01)** collected prior to initiating primary chemotherapy will be a **mandatory requirement** for all patients who are enrolled at GOG or CTSU Institutions, are randomized to have secondary cytoreductive surgery and give permission for their tissue to be used for this research study.

Every attempt should be made to provide a tumor block. If it is not possible to provide a block on a permanent or temporary basis, the back-up option will be to provide sixteen unstained slides, 5 micrometers in thickness, on charged slides suitable for standard immunohistochemistry assays. Tumor block or sixteen unstained slides must be submitted to the GOG Tissue Bank as described in Appendix V to satisfy the FT01 requirement.

If more than one type of fixed tumor will be submitted, please label the tumor specimens sequentially using FT01 for primary tumor tissue and FT02 for metastatic tumor, and contact the GOG Statistical and Data Center to have the additional SP Form for FT02 added to the patient form schedule.

### 7.2112 Recurrent or Persistent Tumor Tissue for Research

The recurrent tumor and possibly normal tissue will be excised during secondary cytoreductive surgery and a portion will need to be fixed in formalin whereas the remainder will need to be frozen (either snap-frozen or OCT-embedded and frozen).

**Formalin-fixed recurrent or persistent tumor (FR01)** will be a **mandatory requirement** for all patients who are enrolled at GOG or CTSU Institutions are randomized to have secondary cytoreductive surgery and give permission for their tissue to be used for this research study. A piece of recurrent or persistent tumor in a jar with formalin must be submitted to the GOG Tissue Bank as described in Appendix V to satisfy the FR01 requirement.

**Frozen recurrent (RR01)** will be a **mandatory requirement** for all patients who are enrolled at GOG or CTSU Institutions are randomized to have secondary cytoreductive surgery and give permission for their tissue to be used for this research study. A snap frozen piece of recurrent tumor wrapped in foil or a piece of recurrent or persistent embedded and frozen in an OCT mold must be submitted to the GOG Tissue Bank as described in Appendix V to satisfy the RR01 requirement.

**Formalin-fixed normal tissue (FN01)** will be an **optional yet high priority requirement** for all patients who are enrolled at GOG or CTSU Institutions are randomized to have secondary cytoreductive surgery and give permission for their tissue to be used for this research study. A piece of normal tissue in a jar with formalin must be submitted to the GOG Tissue Bank as described in Appendix V to satisfy the FN01 requirement.

**Frozen normal tissue (RN01)** will be an **optional yet high priority requirement** for all patients who are enrolled at GOG or CTSU Institutions are randomized to have secondary cytoreductive surgery and give permission for their tissue to be used for this research study. A snap frozen piece of normal tissue wrapped in foil or a piece of normal tissue embedded and frozen in an OCT mold must be submitted to the GOG Tissue Bank as described in Appendix V to satisfy the RN01 requirement.

#### 7.2112 Pathology Slides for Review by the GOG Pathology Committee to Confirm Eligibility

Please see Section 10.3 for details regarding the pathology slides that must be submitted to the Pathology Materials Coordinator in the GOG Statistical and Data Center in Buffalo, New York for review by the GOG Pathology Committee to confirm eligibility for GOG-0213.

### 7.212 Blood Specimens

#### 7.2121 Serum Specimen

**A pre-op serum specimen (SB01)** will be **an optional requirement** for all GOG-0213 patients who are enrolled at GOG or CTSU Institutions are randomized to undergo secondary cytoreductive surgery and consent to allow their blood to be drawn and used to prepare serum for submission and use for this research study. The pre-op serum specimen will be prepared after obtaining consent for this research study but prior to undergoing secondary cytoreductive surgery from 7-10 ml of blood drawn into a **plain red-top Vacutainer® tube** and shipped to the GOG Tissue Bank as described in Appendix V.

#### 7.2122 Plasma Specimen

**A pre-op plasma specimen (PB01)** will be **an optional requirement** for all GOG-0213 patients who are enrolled at GOG or CTSU Institutions are randomized to undergo secondary cytoreductive surgery and consent to allow their blood to be drawn and used to prepare plasma for submission and use for this research study. The pre-op plasma specimen will be prepared after obtaining consent for this research study but prior to

undergoing secondary cytoreductive surgery from 7-10 ml of blood drawn into a **purple-top (violet-top) Vacutainer® tube containing the anti-coagulant EDTA** and shipped to the GOG Tissue Bank as described in Appendix V.

## 7.22 Creation of Tissue Microarrays (TMAs) for GOG-0213

The GOG Tissue Bank will collaborate with the GOG Statistical and Data Center and the GOG Tissue Utilization Subcommittee to design and create a series of TMAs for GOG-0213 to study markers of recurrence, survival and treatment response or resistance. The specific types of the TMAs that can be created will depend on the paraffin block submissions for this protocol and the clinical outcomes observed for these cases. For example, one TMA could contain matched cores of tumor collected prior to initiating first-line and second-line therapy with adjacent normal tissue from secondary cytoreductive surgery whereas another TMA could represent tumor cores from patients who experienced short survival, intermediate survival or long survival or include tumor cores from patients treated on a specific treatment arm who experienced short, intermediate or long progression-free survival.

## 7.23 Laboratory Testing

Unstained sections from conventional blocks and TMAs and aliquots of the pre-op serum specimen will be distributed to Dr. Michael Birrer at the National Cancer Institute for biomarker, proteomic and genomic analyses. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the GOG-0213 tissue specimens and/or the pre-op serum specimen will be reevaluated based on evolving data in the field. All bioinformatics and statistics will be performed as a collaboration between NCI and the GOG Statistical and Data Center.

### 7.231 Light Microscopy

Light microscopy will be performed using formalin-fixed and paraffin-embedded tissue specimens to characterize the histopathologic features of the tissue specimens undergoing molecular and biochemical profiling, and to satisfy some of the specimen election criteria for gene expression profiling. Stained Specimens will be reviewed by Dr William Rodgers (chair of the GOG Pathology Committee) and other members of the Pathology Committee.

### 7.232 Biomarker Analysis

Multiple types of biomarker analyses will be performed to expand our current understanding of the biology, progression, metastasis and responsiveness of recurrent ovarian and peritoneal primary cancer. Immunohistochemistry assays will be performed as needed in sections from conventional paraffin blocks and the GOG-0213 TMAs in Dr Michael Birrer's laboratory at the NCI or by the GOG Receptor Core Laboratory. Reverse phase array and conventional immunoblot analyses

will be performed as needed in lysates from frozen recurrent tumor tissue, microdissected recurrent tumor cells and normal tissue. Quantitative RT-PCR will be performed as needed using specific primers in RNA extracted from the appropriate type of tissue specimens. These assays will be used to identify and/or validate prognostic or predictive markers of recurrent, survival and treatment response or resistance. In addition, these assays will be used to validate individual markers identified in gene expression microarray studies (see below).

7.233 **Genomic Profiling**

Gene expression microarray analysis will be undertaken using RNA isolated from frozen recurrent tumor and normal tissue to define gene expression patterns associated with disease progression, spread of disease, response to treatment or patient outcome. These studies will utilize an affymetrix platform and will be performed in Dr Michael Birrer's laboratory at the NCI. His laboratory has extensive experience in profiling ovarian cancers and will be supported by the Intramural Research Program.

7.234 **Proteomic Profiling**

Proteomic profiling will be performed in pre-op serum specimens to define protein/peptide fragment patterns that are associated with disease progression, spread of disease, and response to treatment or patient outcome. All proteomic studies will be performed by the NCI proteomic group in collaboration with the FDA.

7.3 Quality of Life:

7.31 Patients in the secondary cytoreduction arm will complete the quality of life questionnaire packet (which includes the FACT-O and the RAND SF-36 physical functioning questionnaire) before surgery and before the first cycle of chemotherapy. The FACT-O is available in Spanish and French. Requests should be submitted to the Quality of Life Chair on the protocol: Karen Basen-Enquist, PhD (kbasenen@mdanderson.org) and Lari Wenzel, PhD (lwenzel@uci.edu). Patients in the no surgery arm will complete the quality of life questionnaire packet before the first cycle of chemotherapy. Follow-up questionnaires will be completed prior to beginning of the third cycle (approximately six weeks from the start of treatment) and prior to beginning of the sixth cycle (or approximately 15 weeks from the start of treatment). Additional quality of life assessments will be done at six and twelve months after initiating chemotherapy. If a patient progresses or is removed from the study treatment, continue to follow the schedule of QOL assessments when possible regardless of subsequent treatments. Whenever possible, QOL questionnaires should be administered at the clinic visit before the patient is seen by the physician and before evaluations (e.g., results of CA-125 or scans) are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.32 The Quality of Life Liaison (Nurse\Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.33 The Nurse\Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.

7.34 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.35 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing patient's response.

7.36 Review the questionnaire for completeness before the patient leaves.

7.37 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.38 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.39 It is essential that questionnaires be completed according to the schedule described in Section 7.1.

7.310 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

7.311 The patient may withdraw from the quality of life section of the protocol for any reason. The reason must be documented on the form.

7.312 The Quality of Life Liaison may attend a training session held at a biannual GOG meeting.

## 8.0 EVALUATION CRITERIA

### 8.1 Parameters of Response – GOG RECIST Criteria

8.11 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

8.13 Best Response

Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline. *Reporting of these changes in an individual case should be in terms of the* ***best response*** *achieved by that case since entering the study.*

8.131 Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart. Normalization of CA125, if elevated at baseline, is required for ovarian carcinoma studies.

8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.

8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 8 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.

8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

8.135 Stable Disease is any condition not meeting the above criteria.

8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.

8.14 Progression (measurable disease studies) is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

- or -

- Patients with elevated CA-125 pretreatment, which never normalizes during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

- or -

- Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). Date of progression will be the date of the first confirmatory CA-125 level.

8.15 Progression (non-measurable disease) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Progression based on serum CA-125:
  - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

  - or -

  - Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

  - or -

  - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

  When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). Date of progression will be the date of the first confirmatory CA-125 level.

8.16 Recurrence (following CR) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence

- Increase in serum CA-125 levels as follows:
  - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

8.17 Survival is the observed length of life from entry into the study to death or the date of last contact

8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.

8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.

8.19 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v3.0.

## 9.0 DURATION OF STUDY

9.1 Patients will remain on the designated study regimen until disease progression or toxicity precludes further treatment or the patient refuses study treatment.

9.2 All patients will be followed (with completion of all required case report forms) until disease progression, or the patient withdraws consent. In addition, following disease progression, patients will be monitored for delayed toxicity and survival for a period of 10 years with Q forms submitted to the GOG Statistical and Data Center, unless patient's consent is withdrawn.

# 10.0 STUDY MONITORING AND REPORTING PROCEDURES

## 10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT

### 10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

This study will utilize the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading specific adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page at http://ctep.cancer.gov/reporting/ctc.html. A GOG CTCAE v3.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested.

### 10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

### 10.13 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | Unexpected | Expected |
| **Unrelated** | Not | Not | Not | 7 Calendar | Not | 7 Calendar | Not | 7 Calendar | 7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Unlikely** | Required | Required | Required | Days | Required | Days | Required | Days | Calendar Days |
| **Possible Probable Definite** | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days | 7 Calendar Days | Not Required | 24-Hrs; 3 Calendar Days | 7 Calendar Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under section entitled "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND."**

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**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) with the exception as listed below (grade 2-4 myelosuppression) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- *"All Grades 2, 3 and 4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) regardless of the need for hospitalization is exempt from expedited reporting."*

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The NCI guidelines for expedited adverse event reporting requirements are also available at this site. Please consult these guidelines for secondary malignancy (including AML, MDS) reporting requirements.

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AEs within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP's clinical experience with this agent and defines "expected" Grade 2 and 3 AEs not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com.

10.15 Automated CDUS reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except: F-form, Pathology report, OP report and QOL forms should be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). Quality of Life questionnaires are to be completed on Scantron forms and submitted by mail. Pathology material (F-form, path report and slides) should be submitted together via mail.

| Form± | Due within | | Copies * | Comments |
|---|---|---|---|---|
| | Weeks | Event | | |
| Form R and Form OS-R | 4 | Registration | | Submit via SEDES± |
| Specimen Consent Application | 1 | Registration° | | Complete Online |
| Form DR | 4 | Registration | | Submit via SEDES± |
| Form D2M | 4 | Registration | | Submit via SEDES± |
| Form BDR | 4 | Registration | 2 | Submit to SDC by US Post |

| | | | | |
|---|---|---|---|---|
| Primary Disease<br>Form F<br>Pathology Report<br>Pathology Slides<br>Secondary Cytoreductive Surgery<br>Form F<br>Pathology Report | <br>6<br>6<br>6<br><br>6<br>6 | <br>Registration<br>Registration<br>Registration<br><br>Surgery***<br>Surgery*** | <br>3<br>3<br>**<br><br>3<br>3 | Submit together to the SDC via postal mail<br><br>Submit together to the SDC via postal mail |
| Form C and op report for Cyto reductive Surgery | 6 | Surgery*** | | Submit via SEDES± |
| Form SP-FT01-0213 for archival formalin-fixed and paraffin-embedded primary or metastatic tumor (FT01):<br>1st choice: Block<br>2nd choice: 16 Unstained Slides | 8 | Registration | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-SB01-0213 for pre-op serum submitted frozen in up to ten cryogenic vials | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-PB01-0213 for pre-op plasma submitted frozen in up to ten cryogenic vials | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-FR01-0213 for formalin-fixed recurrent or persistent tumor submitted in a jar | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-RR01-0213 for frozen recurrent or persistent tumor submitted as a piece of snap frozen tissue or a frozen OCT mold | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-FN01-0213 for formalin-fixed normal tissue submitted in a jar | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form SP-RN01-0213 for frozen normal tissue submitted as a piece of snap frozen tissue or a frozen OCT mold | 1 | Surgery*** | | Submit via SEDES for all patients randomized to undergo secondary cytoreductive surgery ∇ |
| Form T-post op**** | 2 | Surgery*** | | Submit via SEDES± |
| Form D2R-Cycle 1<br>Subsequent cycles | 2<br>2 | Completion of each cycle of therapy | | Submit via SEDES±, # |
| Form T | 2 | Beginning of each subsequent cycle | | Submit via SEDES±, # |
| Form D2M | 2 | Clinical response assessment | | Submit via SEDES±, # |
| | | | | |
| FACT-O**** | 2 | Prior to surgery | 1 | If randomized to surgery |
| FACT-O**** | 2 | Prior to cycle 1, 3 and 6 and at 6 and 12 months | 1 | See Appendix III |

| | | | | |
|---|---|---|---|---|
| | | after study entry. | | |
| Form SRGSTAT | 8 | Any major surgical procedure (other than randomized cyto-reductive surgery) while on study and upon completing the study treatment | | Submit via SEDES± |
| Form Q0 | 2 | Completion of study treatment | | Submit via SEDES± |
| Form Q | 2 | Disease progression, death, and post-treatment follow-up | | Submit via SEDES± quarterly for 2 years, semi-annually for 3 more years, yearly thereafter |

* The number of required copies including the original form which must be sent to the Statistical and Data Center. No copies are required for forms submitted through SEDES. Forms submitted through SEDES should not be sent through postal mail or fax.

** Pathology slides are required for central review by the GOG Pathology Committee. At least one representative stained slide (or slides) documenting the primary site, histologic cell type, grade, and one slide to show the most advanced stage of disease. When submitting pathology material to the GOG SDC, individual slides must be labeled with GOG Patient ID and patient initials and packed in plastic slide cassettes. Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Ship pathology slides and three copies of both the Pathology Form F and the official pathology report directly to the Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263; phone (716) 845-5702GOG SDC. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name.

*** Patients who are randomized to surgical cytoreduction, submit after surgery.

**** Submit original Scantron QOL forms and coversheet to the GOG Statistical and Data Center. The patients randomized to cytoreductive surgery undergo an assessment prior to surgery as well as prior to initiating chemotherapy.

± Use the SDC Electronic Data Entry System (SEDES), available on the GOG website, to view and print a copy of each form along with instructions, and to submit forms electronically.

\# In the event that it becomes necessary to modify the dose or stop individual study agents for either protocol directed reasons or other reasons, continue to submit D2R, T and D2M forms until all study agents are stopped or another anti-cancer therapy is initiated.

° Required only for patients randomized to undergo secondary cytoreduction surgery.

▽ SP Forms for all research specimens (mandatory and optional) must be submitted online to the GOG SDC using SEDES for each patient randomized to undergo secondary cytoreductive surgery regardless of whether or not the specimens will be submitted for research. Research specimens must be shipped to the GOG Tissue Bank in Columbus Ohio (address provided below) with copies of the SP Forms as specified in Appendix V. GOG Tissue Bank / Protocol GOG-0213, Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2810, FAX: (614) 722-2897, E-mail: gogbank@pediatrics.ohio-state.edu.Mandatory specimen requirement only for patients undergoing secondary cytoreduction and who provided consent. Submit this SP Form using SEDES.

▽▽ Optional but high priority specimen requirement only for patients undergoing secondary cytoreduction and who provided consent. Submit this SP Form using SEDES.

This study will be monitored by the **Abbreviated/Complete** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

## 11.0 STATISTICAL CONSIDERATIONS

### 11.1 Randomization

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies:

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 **CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment (CTB).

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.13 No cytoreductive surgery

11.14 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments. For those who consent to have cytoreductive surgery determined through randomization, the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study.

### 11.2 Measures of Efficacy and safety

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

### 11.3 Treatment efficacy

*Overall type I error:* This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

*Expected median survival on the standard treatment:* Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane

regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

*Accrual target for evaluating the efficacy of systemic therapy*
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

*Statistical power for evaluating the efficacy of biologic therapy*: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: $H_{01}$: $\Delta_{01} = \lambda_{CTB} / \lambda_{CT} \geq 1$ will be assessed, where $\lambda$ is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their assigned treatment. The type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months).

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

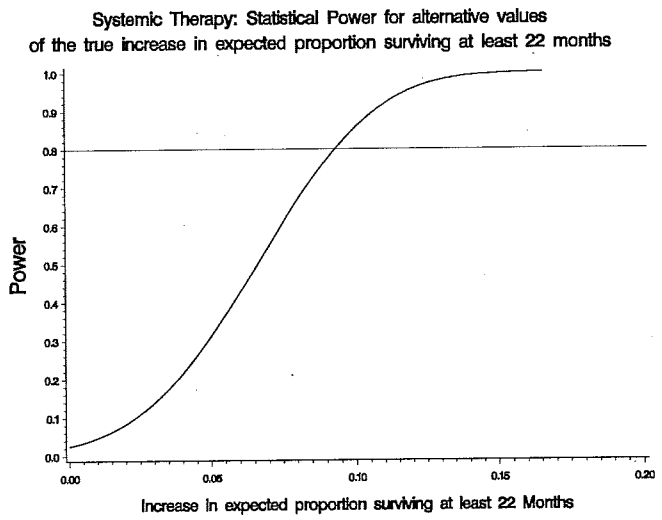


**Figure 1.**

*Statistical Power- evaluating the efficacy of surgical cytoreduction*: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival ($H_{02}$: $\Delta_{02} = \lambda_{\text{surgery}} / \lambda_{\text{No surgery}} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment assignment (CT vs CTB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12 months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses.

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, $H_{02}$, when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2.

The proportion of patients enrolled onto this study, who will be candidates for surgical cytoreduction and consent to having their surgical intervention determined by randomization, is unknown. If 50% of all enrolled patients participate in the surgical component of this study then there will be approximately 214 deaths reported in this subset of patients (660*0.50*0.65, assuming surgery has no effect on overall survival) when the study is considered sufficiently mature for a final analysis of the systemic therapies (objective 1). On the other hand, if only 30% participate in the surgical component of this study then the expected number of deaths reported at this time will be 129.

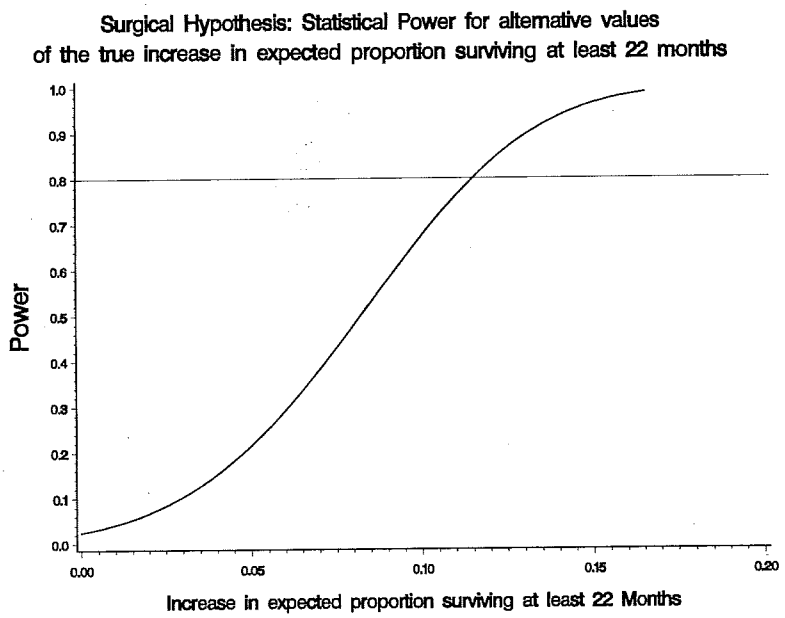


**Figure 2.**

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin (ARM 1). It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.

*Interim Analyses:* Interim analyses are planned when there are at least 110 deaths reported among all those patients allocated to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and July each year and the precise date of these meetings is set without confidential knowledge of the study results.

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information

time, $H_{01}$ will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis.

$H_{02}$ will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of $H_{02}$ will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for $H_{01}$ (or $H_{02}$) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $\Delta_{01} > 1.0$ (or $\Delta_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%.

The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

*Final analysis:* The study will be considered sufficiently mature to permit a final assessment of $H_{01}$ when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of $H_{02}$ when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

*Supplemental final analyses:* A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with

and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

*Safety Analyses:* The GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities, serious adverse event (SAE) reports and deaths in which study treatment may have been a contributing cause. This committee does not review efficacy results. The DSMB may recommend study amendments pertaining to patient safety.

Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

## 11.4 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

*Construct and content*

The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items)[43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

*Descriptive analyses of baseline QOL scores*
Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean, standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

*Differences in FACT-TOI scores between patients receiving CT and CTB:* Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

*Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:*
This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

*Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery.* This analysis will include those patients who were candidates for surgery and consented to have their surgical

intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

## 11.5 Translational Research Statistical Considerations

*Overview*

The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

*Anticipated sample size for translational objectives*

The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately 198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1. Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

*Training and validation set*
In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.

*Identifying biologic/molecular profiles*
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

*Reliability*
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which can not be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

*Validation*
Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in

which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is know to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators, since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.6 The anticipated distribution of patients' race and ethnicity for the systemic therapy portion of this trial is (all are female):

| | |
|---|---|
| White (not Hispanic) | 584 |
| Black (not Hispanic) | 39 |
| Hispanic | 14 |
| Asian | 17 |
| American Indian or Alaskan Native | 3 |
| Native Hawaiian or other Pacific Islander | 3 |

## 12.0 BIBLIOGRAPHY


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TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: SEPTEMBER 29, 2014

RE: PROTOCOL GOG-0213 – REVISION # 12

**Protocol Title:** "A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)"

NCI Version June 23, 2014

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

*Although there is modified risk information for bevacizumab, CTEP has indicated that **the added risks are very similar to or associated with risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD)**. In this case, (1) watering eyes is associated with allergic rhinitis; (2) wound complication is a more general term and includes wound dehiscence; (3) dehydration is associated with other known AEs such as colitis, nausea, and vomiting; (4) infections, other (necrotizing fasciitis) is a specific type of infection, a previously identified risk; (5) an increase in frequency of neutrophil count decreased resulted in this risk being moved from less likely to likely, but this risk was previously identified; (6) an increase in frequency of platelet count decreased resulted in this risk being moved from reported but undetermined to less likely, but this risk is associated with bone marrow suppression which is already reflected in the increase in frequency of neutrophil count decreased.

**When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised informed consent**

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**document is reviewed and approved by the Investigational Review Board (IRB)**. For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the informed consent; however, changes to the ICDs cannot be implemented until they are approved by the IRB. **Please note that there will be no Action Letter.**

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# SUMMARY OF CHANGES

The following changes are being submitted in response to an RA from Dr. Helen Chen (Helen.chen@nih.gov):

For Protocol Revision #12 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: June 23, 2014
Protocol Date: June 23, 2014

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1 | NCT# 00565851 has been added.<br>NCI version date has been updated.<br>Includes Revisions #1-12.<br>Lead Institution and Participation Organizations have been added.<br>Heather Lankes has replaced Kathleen Darcy as Translational Research Scientist.<br>Revised footer has been added. |
| | 4.36 | 32-37 | A Revised CAEPR (Version 2.3, August 1, 2013) has been inserted.<br>• Added New Risk:<br>  • Less Likely: Dehydration; Wound complication<br>  • Rare But Serious: Infections and infestations – Other (necrotizing fasciitis)<br>  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (tympanic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyramidal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular pucker); Eye disorders – Other (transient increased IOP > or = 30 mm Hg); Eye disorders – Other (vitreous hemorrhage); Eye pain; |

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| # | Section | Page(s) | Change |
|---|---|---|---|
| | | | Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperthyroidism; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor pain; Typhlitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain<br>• <u>Increase in Risk Attribution:</u><br>  • <u>Changed to Likely from Less Likely</u>: Neutrophil count decreased<br>  • <u>Changed to Less Likely from Reported But Undetermined</u>: Platelet count decreased<br>• <u>Decrease in Risk Attribution</u>:<br>  • <u>Changed to Reported But Undetermined from Less Likely</u>: Vertigo<br>• <u>Provided Further Clarification</u>:<br>  • Supraventricular tachycardia is now reported as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, "Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter."<br>  • Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the following footnote (#10) was added, "Anastomotic leak may include Gastrointestinal anastomotic leak; |

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| # | Section | Page(s) | Change |
|---|---|---|---|
| | | | Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak."<br>• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:<br>  • Added: Dehydration; Platelet count decreased; Wound complication<br>• Deleted Risk:<br>  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothorax |
| 2 | 5.1 | 44 | This section has been updated with OPEN language for patient entry and registration. |
| 3 | 10.1-10.3 | 77-85 | References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol. |
| | ICD | | Additional changes have been made to the IC document. |

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PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)**(12/19/2011) (10/01/12)NCT# 00565851**

*NCI Version 06/23/2014*

Includes Revisions #1-12

POINTS:

PER CAPITA –14

MEMBERSHIP –6 and 6 additional if surgical candidate is randomized

TRANSLATIONAL RESEARCH PER CAPITA – Award up to 6.5 points based on specimen submissions. Distribution:

- Archival fixed and embedded primary or metastatic tumor (block or 16 unstained slides)-1 point,
- Frozen recurrent tumor-1 point
- Fixed recurrent tumor in a jar of formalin or embedded in a paraffin block-1 point
- Frozen normal tissue-0.5 point
- Fixed normal tissue in a jar of formalin or embedded in a paraffin block-0.5 point
- Frozen pre-op serum-0.5 point
- Frozen pre-op plasma-0.5 point
- Whole blood-0.5 point (for all patients not just patients randomized to surgery)**(06/22/09)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for **submission of satisfactory** fixed primary tumor, frozen recurrent tumor, fixed recurrent tumor, frozen serum and frozen plasma.

Lead Institution: NRG/NRG Oncology

**Participating Organizations ()**
**ALLIANCE** / Alliance for Clinical Trials in Oncology
**ECOG-ACRIN** / ECOG-ACRIN Cancer Research Group
**SWOG** / SWOG

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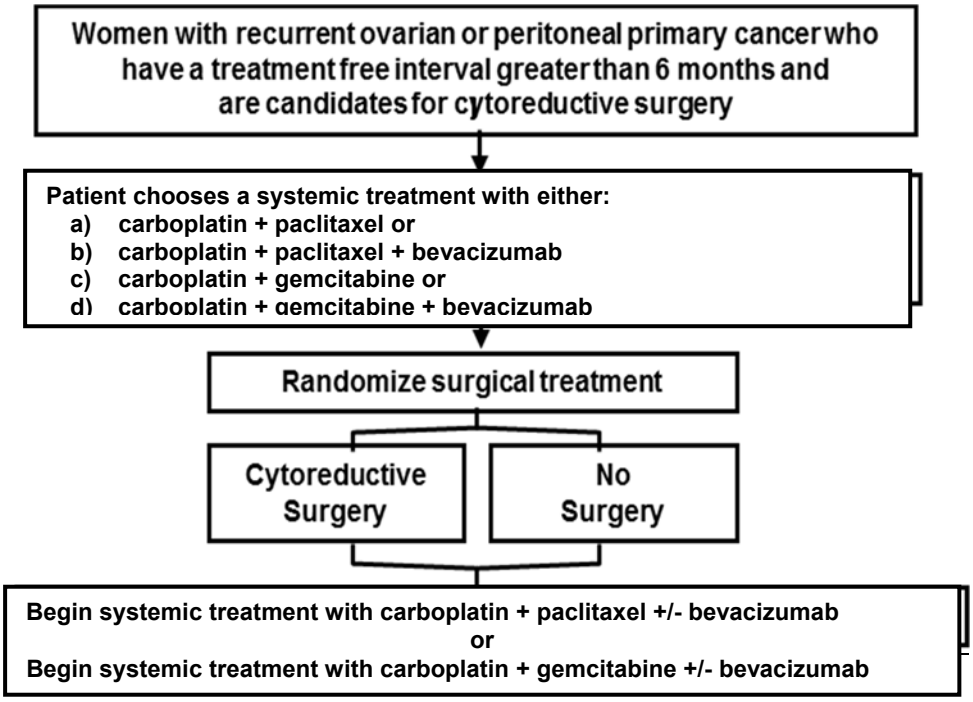
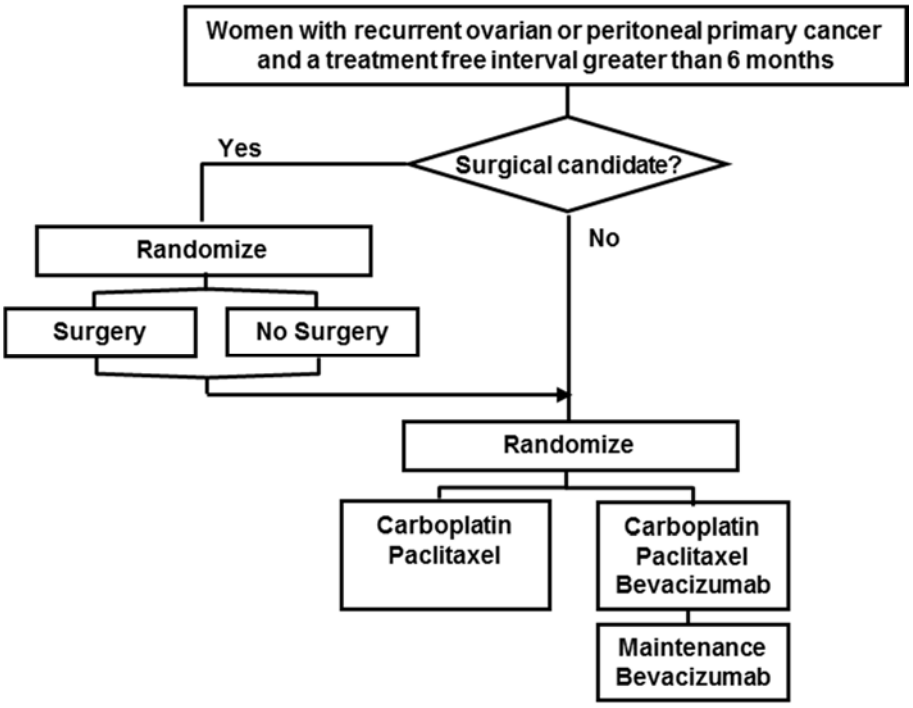
OPEN TO PATIENT ENTRY DECEMBER 06, 2007; REVISED AUGUST 4, 2008; REVISED JUNE 22, 2009; REVISED MARCH 15, 2010; REVISED AUGUST 23, 2010; REVISED JANUARY 3, 2011 REVISED AUGUST 29, 2011; REVISED SEPTEMBER 26, 2011; REVISED DECEMBER 19, 2011, REVISED OCTOBER 1, 2012; REVISED AUGUST 19, 2013; REVISED SEPTEMBER 29, 2014

**SCHEMA beginning 8/29/2011(08/29/11) (12/19/11)(10/01/12)**




The following schema was in effect between 12/6/2007 to 8/28/2011. Once the accrual goal for evaluating the chemotherapy regimens was attained, that randomization was eliminated and only the surgical randomization remains (see the schema above).**(08/29/11)(12/19/11)**

SCHEMA **(06/22/09)**



Please see Section 7.32 and Appendix III (Specimen Procedures) for details regarding the specimen requirements and laboratory testing for this protocol. Archival tumor, tissue specimens from secondary cytoreductive surgery and two tubes of blood (to make serum and plasma) will only be required from women randomized to surgery and who consent to allow their specimens to submitted and used for this research study. A new specimen requirement was added to this protocol. The collection of whole blood will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0213. Women already enrolled on GOG-0213 will need to be re-consented for this collection. If the patient does not give permission, select "No" in the online Specimen Consent Application for the question "Did your patient give permission for her blood to be collected for submission and use for this research study" and enter "patient refusal" as the reason the specimen was not collected/submitted in item 5 on the SP Form for WB01.

Post surgical randomization treatment options now include either paclitaxel or gemcitabine in combination with carboplatin. Either chemotherapy doublet may be administered with bevacizumab at the discretion of the investigator. If chosen, bevacizumab maintenance is given until disease progression or unacceptable toxicity.**(10/01/12)**

TABLE OF CONTENTS (08/04/08) (06/22/09)

## 1.0 OBJECTIVES

### 1.1 Specific Hypotheses: **(08/04/08)**

Two principle hypotheses will be directly addressed in this randomized, phase III clinical trial in recurrent platinum-sensitive ovarian, peritoneal primary or Fallopian tube cancer patients.

1.11 Surgical secondary cytoreduction prior to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.12 The addition of bevacizumab to second-line paclitaxel and carboplatin and maintenance phases of treatment increases the duration of overall survival relative to second-line chemotherapy alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary, or Fallopian tube cancer.

### 1.2 Primary Objectives:

1.21 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.22 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of overall survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

### 1.3 Secondary objectives: **(08/04/08)**

1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.

1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

1.34 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases QOL relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian, peritoneal primary or Fallopian tube cancer.

1.4 Translational Research Hypotheses **(08/04/08)**

The following translational research hypotheses will be tested in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.

1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.5 Translational Research Objectives **(08/04/08)**

The following translational research objectives will be evaluated in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.

1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.53 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.**(06/22/09)**

## 2.0 BACKGROUND AND RATIONALE

### 2.1 Rationale for Selected Approach and Trial Design

Ovarian cancer remains the most lethal primary gynecologic malignancy in the United States. This year over 16,000 women will die from their disease. The principle reason for this outcome is disease recurrence and the emergence of drug resistance. Patients with recurrent disease frequently undergo multiple cycles of multiple drug regimens. Those fortunate to achieve a response to chemotherapy are however, rarely cured and find that their remission cycles are short-lived. Even if a complete response is re-achieved it is usually of a shorter duration than the first disease-free interval. Those not achieving a response to recurrence therapy live less than 2 years. While effective therapy following disease recurrence is a major unmet need, few interventions have successfully altered the natural history of recurrence. We propose to address two important interventions, surgery and combination chemotherapy with biologics, neither previously studied in a prospective randomized design, in order to determine their impact on survival.

### 2.2 Rationale for Surgery

The capacity of cytoreductive surgery to improve survival for patients with advanced, newly diagnosed epithelial ovarian cancer is generally accepted.[1] However, the role of tumor-reductive surgery for patients with recurrent disease continues to evolve.[2] Several series have demonstrated the importance of tumor reductive surgery prior to the initiation of second-line chemotherapy.[1, 3, 4] Preliminary results indicate a maximal survival benefit for patients rendered visibly disease-free prior to second-line therapy.[1, 4, 5] The frequency of reported optimal operative outcomes has ranged from 37% to 83% in small series, using various criteria for "optimal cytoreduction".[6] The relative importance that differences in study cohorts, attitude, technical capability and experience have in accounting for variation of operative outcomes is unknown. In a recent series, the largest yet published, approximately 80% of the patients had complete cytoreduction.[5] Clinical criteria such as the median age, median disease-free interval, amount of prior chemotherapy, performance status, size of intra-abdominal disease, and locations of disease suggests patients in that series to have disease at least as advanced as other reports.[1, 3, 4, 7] That investigation prospectively demonstrated that secondary cytoreductive surgery, followed by salvage chemotherapy, allows survival that is significantly improved. The 34.4 month overall median survival from the time of secondary operation and the 35.9 month overall median survival from the time of recurrence in the most recent series exceed what is typically reported in the salvage chemotherapy literature. Another noteworthy observation from this study was that the median survival after diagnosis of recurrence for patients who did not have salvage chemotherapy before secondary operation (48.4 months) dramatically exceeded the overall median survival for those who were pretreated (24.9 months).

Furthermore, an estimated 40% of the patients operated on before administration of salvage therapy survived more than five years after recurrence compared to only 15% in the pretreated group. Of note, patients whose disease responded to a recent repeat course of platinum containing agents, and patients treated with non-platinum containing agents before secondary operation, both had poor survival, that did not remotely approach the overall group who had secondary cytoreductive operations prior to salvage chemotherapy. Perhaps pretreatment with salvage chemotherapy induces drug resistance. Regardless, limiting the role of surgery to palliation of symptoms for patients who failed multiple salvage regimens and the strategy of treating with salvage chemotherapy before an attempt at secondary cytoreductive surgery may greatly diminish the chances for subsequent survival. Confirmation of this observation within the context of a multi-center randomized trial may dramatically improve the survival potential for women with recurrent epithelial ovarian cancer.

## 2.3 Rationale for Combination Chemotherapy (10/01/12)

Most patients medically suitable to undergo therapy at the time of recurrence will be offered chemotherapy. To date, a limited number of agents (i.e. etoposide, liposomal doxorubicin, topotecan, etc) have been formally approved for administration in this setting. In addition, several other agents have been studied and are documented to have clinical activity. Joining these novel agents are the taxanes and platinates commonly used as standard therapy in the front-line setting. In light of this expansion of potentially active chemotherapeutics, physicians are administering more agents, longer to more patients. Nonetheless, the degree to which this practice is benefiting patients in terms of survival is unclear.

An additional challenge lies in how to determine when to recommend which agents or combinations to patients with recurrent disease. A common determinant for many clinicians lies in reference to the patient's time in remission following front-line therapy. Those disease-free for more than six months are commonly considered to be potentially sensitive to retreatment with platinum. Response characteristics with single agent platinum in this setting produce results similar to patients treated with novel agents. Patients with longer disease-free interval are commonly treated with combination platinum and taxane therapy similar to the regimens received as primary therapy. The degree to which this philosophy of care has affected survival is unknown but data from the limited number of randomized trials would suggest the following:

- Non-platinum novel agents such as topotecan, gemcitabine, liposomal doxorubicin, and paclitaxel have similar response and survival characteristics as compared to platinum in randomized phase III trials.
- No difference in response has been observed in these novel agents among platinum sensitive or resistant patients. However, treatment with liposomal doxorubicin demonstrated a survival benefit in comparison to topotecan in the

absence of a response benefit among patients with platinum-sensitive disease.[8] The reasons for this are not clear but may relate to either intrinsic drug activity or to trial design (limited availability to liposomal doxorubicin in topotecan failures).

- Platinum, and platinum combinations have favorable response characteristics in platinum-sensitive patients.[9, 10] Platinum and taxane combination therapy appears to be at least as effective as single agent platinum and data from one large phase III trial would suggest clinical superiority.[11] Although the randomized population in that trial was dissimilar to those commonly treated in the US, a second randomized phase II clinical trial in a more selective population essentially confirmed the observed benefit.[12] Further, a randomized clinical trial of gemcitabine and carboplatin demonstrated superiority in progression-free survival over carboplatin alone in platinum-sensitive patients.[13] Although a survival benefit was not demonstrated, the trial was underpowered to address this endpoint.
- Recently, gemcitabine, carboplatin and bevacizumab was compared to gemcitabine and carboplatin demonstrating further enhancement in progression-free survival (12.4 mos vs 8.4 mos, HR 0.48, 95% CI:0.39-0.61), response rate (79% vs 57%, p<0.0001) and duration of response (10.4 mos vs 7.4 mos, 95% CI: 0.41-0.70). Although immature at the time of reporting, there was no overall survival benefit with nearly 50% of events recorded.[73]

From these observations, it would appear the greatest activity and potential for survival enhancement lies in combination, platinum-based chemotherapy among those deemed potentially platinum (and taxane) sensitive. As demonstrated above, a survival benefit is also suspected in this cohort for surgery. A randomized trial is needed to evaluate the addition of surgery to combination therapy to determine their impact on survival.

2.31 Docetaxel

Taxanes are a class of anticancer agents that exert cytotoxic effects by their unique inhibition of microtubular assembly by stabilizing tubulin polymerbundles.14, 15 Both paclitaxel and docetaxel belong to the taxane family and have demonstrated activity in tumors that are refractory to conventional chemotherapy regimens. Paclitaxel is a diterpene plant product derived from the bark of the Western yew (Taxus brevifolia), while docetaxel is a semisynthetic derivative of 10-deacetylbaccatin III, a compound extracted from the needles of the European yew (Taxus baccata). While the relative efficacy of paclitaxel and docetaxel has not been compared clinically, docetaxel has increased activity in vitro, as well as clinical activity in paclitaxel resistant tumors.

**In Vitro Activity**.
The cytotoxicity of docetaxel in comparison with paclitaxel was evaluated

in several murine and human long-term cell culture lines. Docetaxel was found to be generally more cytotoxic (1.3-12-fold), a result that could be explained by its higher achievable intracellular concentration, its higher affinity for microtubules, and its slower cellular efflux.[14-21]Furthermore, docetaxel affects centromere organization resulting in abortive mitosis.[22] These cellular events may account for the greater cytotoxicity of docetaxel compared to that seen with paclitaxel. In terms of cross-resistance with other antitumor agents, there was cross-resistance to docetaxel in multidrug-resistant sublines such as P388/DOX3, CEM/VLB 1000 and Chinese hamster ovary AUXB1 line.[23] However, no cross-resistance to docetaxel was observed in CHO cells expressing a low level of vincristine-resistance but P-glycoprotein positive.[23] This means that cross-resistance to docetaxel was not definitively observed in sublines expressing the MDR phenotype.[24]These findings were in agreement with cell line studies showing that docetaxel was active in paclitaxel-resistant cells.[16]In addition, there was a lack of cross-resistance to cisplatin in certain cell lines.[17,22]

**Efficacy in Murine Tumor Models**

In a murine tumor model with B16 melanoma, docetaxel demonstrated clear superiority to paclitaxel, having a 2.7 times greater log cell kill than paclitaxel.[25] Docetaxel at a dose of 100 mg/m$^2$ has demonstrated significant activity with response rates of 23-40% as second-line therapy in platinum resistant ovarian carcinoma.[26-28] More recently, its activity in paclitaxel-resistant tumors has been studied. The use of docetaxel at a dose of 100 mg/m$^2$ every 21 days in paclitaxel-resistant breast cancer has demonstrated a 17.5% response rate in 41 evaluable patients.[29] Additionally, the use of docetaxel at this same dose in paclitaxel-resistant ovarian cancer has recently demonstrated a 37.5% response rate in 8 evaluable patients.[30] The in vitro, in vivo and clinical data make docetaxel an excellent agent to evaluate after primary platinum and paclitaxel therapy. Hematologic toxicity is the dose-limiting toxicity, with neutropenic fever occurring in 8- 48% of patients.[26-28]Hematologic toxicity is considerably more severe with poorer hepatic function.[31]A comparative study of patients with or without liver dysfunction treated with docetaxel at a dose of 100 mg/m$^2$ was recently reported. Patients with impaired liver function defined as an SGOT or SGPT > 1.5 x upper limit of normal or alkaline phosphatase > 2.5 x upper limit of normal, had a higher rate of neutropenic fever 23.8% vs 12.9% (p=0.06) and toxic death 11.9% vs 1.7%, (p=0.001). For that reason strict criteria for hepatic function are required for this study.

**Efficacy in Humans**

Several phase II and one randomized phase III trial have been conducted evaluating clinical efficacy of docetaxel in primary and recurrent ovarian cancer. Rose et al., reporting on behalf of the GOG, demonstrated a

22.4% overall response rate (5% CR and 17% PR) in 60 patients with platinum and taxane resistant recurrent disease (defined as progression on or within 6 months of completion of primary therapy). Docetaxel for this trial was administered at 100 mg/m$^2$. Grade IV hematologic toxicity was observed in 75% of patients at this dose.[32]Similarly, Verschraegen et al., reported a 23% response rate and a median PFS of 3.5 months among 30 assessable patients in a slightly less resistant population. Grade IV granulocytopenia occurred in 72% of protocol patients and like the Rose trial was a reflection of higher docetaxel dosing (100 mg/m$^2$).[30] Markman, evaluated docetaxel (75 mg/m$^2$) in 30 taxane-resistant ovarian cancer patients. In this study, taxane-resistance was defined as progression on or within3 months of paclitaxel therapy. Patients with longer intervals from paclitaxel were to be retreated with that agent – and progressed – prior to docetaxel. In this trial, 3 patients (10%) had an objective response. Hematologic toxicity was reduced (30%, Grade IV), likely a reflection of reduced dosing.[33]

Based on objective clinical activity in these resistant patient cohorts, a randomized clinical trial comparing taxane and platinum combination therapy in front line ovarian cancer treatment was conducted and recently reported. Vasey and colleagues reported similar PFS (15.0 vs 14.8 months, HR: 0.97 (0.83-1.13) and OS rate at 24 months (64.2% vs. 68.9%, HR: 1.13 (0.92-1.39) for the docetaxel/carboplatin combination compared with the industry standard paclitaxel/carboplatin. In this 1077 patient trial toxicity was significantly different with more hematological toxicity seen in the docetaxel combination (Grade III/IV granulocytopenia 94% vs. 84%, $P < 0.001$) but more severe and longer lasting sensory-motor neurotoxicity for paclitaxel/carboplatin (11% vs. 30, $P < 0.001$).[34]These trials establish clinical efficacy and safety for docetaxel and suggest possible non-cross resistance with paclitaxel. Given the lack of a clear dose response for this agent we propose to utilize 75 mg/m$^2$ to initiate the trial.

## 2.4 Rationale for Angiogenesis Targeted Therapy

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells and normal endothelial cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[35-38]A strong relationship exists between the expression of angiogenesis biomarkers and the behavior of epithelial ovarian cancer, suggesting pharmacological inhibitors of angiogenesis could arrest tumor progression.[39, 40]Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[41] Bevacizumab is a recombinant humanized version

of a murine anti-human VEGF monoclonal antibody, named rhuMAb VEGF. Bevacizumab has been advanced into clinical development for use as a single agent to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to disease progression in patients with metastatic solid tumors.[42] A recent phase II trial of single agent bevacizumab for patients with recurrent, platinum/taxane refractory epithelial ovarian and peritoneal primary cancer has been reported in the GOG (GOG-0170D). Sixty-two women were enrolled in the phase II trial, and objective responses were observed in 17.7%.[43]Response duration was 10.3 months. This was an extremely unusual observation for a compound presumed to be at best cytostatic when administered as a single agent. Further exploration in combination with chemotherapy is warranted in ovarian cancer patients given the survival benefits observed for bevacizumab-combinations in other solid tumors such as breast, renal, lung and colon cancers.

## 2.5 Rationale for Combination Cytotoxic and Biologic Therapy

Evidence from pre-clinical studies and recent phase II and III clinical trials in other solid tumors has demonstrated enhanced anti-tumor activity of traditional cytotoxic regimens, when combined with bevacizumab. For example, Devore and colleagues reported on a three-arm phase II randomized trial of carboplatin/paclitaxel with or without bevacizumab (7.5 mg/kg or 15 mg/kg dose levels) every 21 days until disease progression, in 99 patients with stages IIIB and IV non-small cell lung cancer. Response rates were 21.9 percent (7/32 patients) in the low dose and 42.9 percent (14/35 patients) in the high dose bevacizumab combination arms, compared to a response rate of 31.3 percent (10/32 patients) in the chemotherapy alone arm. A phase II/III trial in this patient population has been conducted by ECOG; the final analysis of this study is pending.

More importantly, a recently reported phase III trial, AVF2107, of over 800 previously untreated patients with metastatic colorectal cancer randomized to receive either bevacizumab for one year plus the Saltz chemotherapy regimen (5-FU/Leucovorin/CPT-11, IFL) or the Saltz regimen plus placebo for one year met its primary endpoint of improving overall survival. The magnitude of benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary endpoints of progression-free survival, response rate, and duration of response (see following table).

| | **IFL/Bevacizumab (n = 403)** | **IFL/Placebo (n = 412)** | **Hazard Ratio (p-value)** |
|---|---|---|---|
| Response Rate | 44.9% | 34.7% | (0.0029) |
| Median TTP | 10.6 mos | 6.2 mos | (0.00001) |
| Median Survival | 20.3 mos | 15.6 mos | 0.65 (0.00003) |

Bleeding, thrombosis, asymptomatic proteinuria and hypertension were identified in phase II studies as possible safety events, but only Grade 3 hypertension and arterial thrombosis events were clearly increased in this phase III study.

Preliminary results from a more recent, large, randomized phase III trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab in combination with an oxaliplatin regimen known as FOLFOX4 (oxaliplatin, 5-fluorouracil and leucovorin) had a significantly prolonged survival over patients who received FOLFOX4 alone. The Data Monitoring Committee overseeing the trial, known as E3200, recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival, which was 17% longer in the bevacizumab arm. Specifically, the median overall survival in the bevacizumab plus FOLFOX4 arm was 12.5 months compared to 10.7 months for patients treated with FOLFOX4 alone. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone. Treatment toxicities observed in this study were consistent with those adverse effects observed in other clinical trials in which bevacizumab was combined with chemotherapy. These included hypertension and bleeding as more predominant in the bevacizumab arm.

Multiple phase I-III trials, such as those cited above, have demonstrated the safety and tolerability of bevacizumab with traditional schedules and dosing of carboplatin and paclitaxel.

2.6 Gastrointestinal Perforation/Fistula

GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. In various phase II series of bevacizumab in recurrent ovarian cancer the rate of GI perforation has ranged from 0-14%. No phase III randomized trials of bevacizumab alone or in combination with chemotherapy have been conduct heretofore. Review of cases reported to CTEP in an open-label phase II ovarian cancer trial of bevacizumab did not specifically isolate risk factors for this complication; however, most patients were heavily pretreated and had abdominal tumor burden (CTEP IND Action Letter, October 4, 2005). GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, or co-morbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

## 2.7 Rationale for Clinical Trial Design **(10/01/12)**

Bevacizumab was selected for evaluation in combination with standard chemotherapy based on preliminary phase II single agent data obtained in patients with recurrent epithelial ovarian and peritoneal primary cancers and results from a phase III clinical trial in patients with metastatic colorectal cancer demonstrating a survival benefit to patients receiving bevacizumab with standard cytotoxic chemotherapy compared with patients receiving standard chemotherapy alone. Recently, evidence of enhanced progression-free survival was observed for combination bevacizumab with gemcitabine and carboplatin followed by bevacizumab maintenance to progression in women with platinum-sensitive recurrent ovarian cancer.[73]Based on the mechanism of action of bevacizumab, there may be benefit to extended therapy until disease progression, in extending PFS or OS in this patient population. Therefore, combination chemotherapy is compared against combination carboplatin/paclitaxel/bevacizumab or carboplatin/gemcitabine/bevacizumab with bevacizumab maintenance therapy.

## 2.8 Rationale for Evaluation of Hypersensitivity

Expansion of the use of platinum and taxane compounds for the treatment of recurrent disease has ushered in an increasing awareness of problematic drug-specific hypersensitivity reactions (HSRs).[44-48]The syndrome is manifested by flushing, dyspnea/bronchospasm, back pain, chest discomfort, pruritus, erythema, nausea, hypotension and occasionally bradycardia/tachycardia. They are profound experiences for patients. Although reported as early as the 1970's for platinum and the 1980's for paclitaxel, prophylaxis has been unable to completely eradicate these reactions often considered by investigators as severe enough to warrant agent discontinuation. Markman, reporting on 205 patients treated with carboplatin, documented 24 (12%) with HSR occurring after a median of 8 courses. He noted that without prophylaxis, only 1 of 3 patients retreated with the agent were able to undergo infusion.[49]Recently, however, several investigators have reported in small single institution studies the success of retreatment programs for those patients suffering hypersensitivity reactions to either or both carboplatin and paclitaxel. These regimens, which include slower infusion, prolonged and repeated premedication prophylaxis and accelerated dosing over time, have been largely successful. Brown and colleagues reported on 32 patients demonstrating hypersensitivity reactions while undergoing treatment for gynecological malignancies. Twenty-three patients had recurrent ovarian or peritoneal cancer. Reactions to platinum (cisplatin and carboplatin) and paclitaxel were observed. Seventeen patients underwent a desensitization protocol and had re-treatment attempted. Seven out of 8 platinum HSRs and 8 out of 10 paclitaxel HSRs were successfully re-treated following desensitization. Lee and colleagues also reported successful reinfusion of paclitaxel, carboplatin or both in 57 patients (255 courses) using a desensitization protocol. Twelve percent of patients had breakthrough symptoms described as of lower severity than the index event – these were also successfully controlled and enabled subsequent retreatment.[48]

The incidence of hypersensitivity is largely unknown particularly in this era of nearly universal paclitaxel and platinum re-treatment. Estimates range from 2-16% for paclitaxel and 5-20% for cisplatin and carboplatin with the latter being reported with increasing frequency. No prospective trials to date have evaluated this incidence in the recurrent setting. Information will be useful in developing strategies to predict or modify re-treatment to avoid these dramatic complications of infusion.

## 2.9 Rationale for Quality of Life Assessment

The quality of life (QOL) component of this trial has two foci: evaluating the effects of the cytoreductive surgery and assessing the impact of adding bevacizumab to second-line paclitaxel and carboplatin for second-line and maintenance therapy.

The primary QOL question with regard to the surgery randomization is whether cytoreductive surgery is associated with improved quality of life due to its anti-tumor effect. The evaluation of this question is critical because, although cytoreductive surgery has the potential to increase survival and improve QOL through reducing tumor burden, potential surgical complications and recovery from surgery may adversely affect QOL. Thus, secondary cytoreductive surgery may initially produce a decline in quality of life, while patients recover from surgery and complications, followed by an improvement in quality of life due to reduced tumor burden.

With regard to the chemotherapy, the principle QOL question is whether the addition of bevacizumab to second-line carboplatin and paclitaxel, followed by maintenance therapy with bevacizumab is associated with better quality of life than carboplatin and paclitaxel combination therapy. The addition of maintenance treatment may present additional toxicities such as fatigue, rash, and diarrhea.[50-52] These toxicities could affect a range of quality of life areas.

Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) a 37-item questionnaire that measures physical, functional, social, and emotional well-being, along with a subscale that measures concerns specific to women with ovarian cancer. The physical, functional, social, and emotional well-being subscales comprise the FACT-G (General), which is considered appropriate for use with patients with any form of cancer. Version 4 of the FACT-G is widely used and has undergone psychometric testing and demonstrates good reliability and validity consistent with previously published data on earlier versions. In a validation study of the FACT-O (FACT-G subscales plus ovarian-specific subscales), the total scale and subscales demonstrated very good to excellent internal consistency reliability (0.74-0.92) and test-retest reliability (0.72-0.88).[53] Validity of the FACT-O was demonstrated by correlation with other quality of life measures, and by its relationship to performance status,

treatment status, and disease stage. The FACT-O, particularly the physical well-being, functional well-being, and ovarian subscales were sensitive to changes in performance status over a two-three month period. To assess the effects of bevacizumab-related side effects on QOL, questions from the FACIT measurement system have been added related to rash, concerns about appearance, diarrhea, fatigue, and appetite (labeled "Additional Concerns (TSE)".

In order to evaluate the effect of surgery on quality of life, patients will complete the Physical Functioning Subscale of the Rand 36-Item Short Form Health Survey (Rand SF-36). The Physical Functioning (PF) Subscale is a 10-item subscale of the Rand SF-36a global quality of life questionnaire, designed to assess quality of life of patients across all medical conditions [54-56].

The PF Subscale consists of items concerning activities of daily living: walking, climbing stairs, bathing, dressing, and performance of physical activities, with each item rated on a three-point scale of limitation of activity due to the patients' health, from "not limited" to "limited a lot." Internal consistency of the PF subscale is excellent, with an alpha co-efficient ranging from 0.89 to 0.92.[56] The PF subscale has been found to significantly correlate with other physical functioning measures (Sickness Impact Profile [SIP], r=.67-.78; shortened Arthritis Impact Measurement Scale (sAIMS, r=.60). Further evidence of validity was provided by the PF subscale distinguishing between patients with serious and mild medical conditions.[57]Furthermore, the PF subscale has been found to be responsive to changes in functioning after surgical procedures (thoracic surgery for treatment of non-small-cell lung cancer, abdominal aortic aneurysm repair, and total hip arthroplasty [58]), and sensitive to differences in quality of life between laparoscopic and open surgical procedures [59,60] and between epidural and patient-controlled analgesia after colonic surgery.[57] Norms have been developed for all subscales of the SF-36, by gender and age groups, based upon 2,474 respondents, as well as for patients with physical limitations.[58, 59]

Eight questions will be included to measure specific quality of life problems after surgery (labeled "Additional Concerns (S)" in). These questions will address issues such as pain, fatigue, problems with the surgical incision, and ostomy appliances. Similar questions have been used in GOG-0152 (A Phase III Randomized Study of Cisplatin And Taxol® with Interval Secondary Cytoreduction versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III Epithelial Ovarian Carcinoma). Several of the questions were taken from questionnaires in the FACIT quality of life measurement system.[61] others were drafted to be similar in format to FACIT questions.

## 2.10 Background and Rationale for Translational Research**(08/04/08)**

The translational research component of this protocol will focus on the molecular and biochemical phenotype of recurrent ovarian cancer. It is well known that the vast majority of patients with advanced ovarian cancer who respond to initial

therapy will recur. However, these recurrent tumors remain essentially a molecular enigma because of their general unavailability for analysis. A brief review of the GOG Tissue Bank demonstrated that less than 5% of ovarian cancer specimens are from sources other than the primary tumor. Further, only 22 specimens of recurrent ovarian cancer with attached clinical data have been banked.

This protocol provides an extraordinary opportunity to study these tumors, characterize them on a molecular basis, compare them to the original primary tumor, and determine the basis for disease recurrence and altered drug sensitivities. In the past five years, over 600 manuscripts on expression profiling of cancers using microarray technology have been published, illustrating the recognized utility of this approach in exploring questions of tumor biology and clinical correlates. The principles of class prediction and class discovery as they apply to the molecular classification of human cancers were exemplified by Golub et al., who used oligonucleotide microarrays to monitor gene expression in acute leukemias as a test case.[62] Class prediction identified and validated a subset of informative genes whose expression was highly correlated with previously defined classes. Further, subsequent studies have utilized these approaches to provide proof of the "molecular profiling principle" as well as to gain novel insights into clinical cancer problems. Using a specialized, lymphoid cell-specific cDNA microarray, Alizadeh et al. performed expression profiling of diffuse large B-cell lymphomas and identified two molecularly distinct forms of this malignancy that correlated with overall survival.[63]

Further, recent work on the problem of drug resistance has detailed multiple potential biochemical mechanisms, which may be critical for the development of drug resistance in ovarian cancer. For instance the expression level of DNA repair enzymes and membrane transporters have been implicated in cisplatin resistance while microtubule mutations have been shown to affect paclitaxel sensitivity.[64, 65] These *in vitro* determined mechanisms require testing and validation on in vivo derived tumor specimens.

GOG-0213 patients with platinum-sensitive, recurrent epithelial ovarian, peritoneal primary or Fallopian tube carcinoma undergoing secondary cytoreduction will be able to provide archival formalin-fixed and paraffin-embedded primary or metastatic tumor, a pre-op serum specimen, a pre-op plasma specimen, formalin-fixed recurrent tumor, frozen recurrent tumor, formalin-fixed normal tissue and/or frozen normal tissue to establish an enduring resource for defining the molecular and biochemical phenotype of recurrent ovarian cancer. The pre-op serum and plasma will be prepared from blood drawn prior to secondary cytoreductive surgery. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the tissue, serum and plasma specimens submitted for the GOG-0213 patients undergoing secondary cytoreduction will be reevaluated based on evolving data in the field.

2.11 Rationale for Banking DNA from Whole Blood for Research **(06/22/09)**

The National Cancer Institute is encouraging Cooperative Clinical Trial Groups including the Gynecologic Oncology Group to bank whole blood from women participating in clinical trials such that the blood specimens will be linked to clinical outcome data (progression-free survival, overall survival, response and adverse effects) and information regarding treatment. The purpose of this effort is to support research including pharmacogenomic and pharmacogenetic research.

Women who are candidates for this clinical trial or who have already been enrolled on GOG-0213 will be asked to give permission for 10 ml of their blood to be collected for this research study and for future research. No matter what the women decide to do, it will not affect their care. The women can still participate in this GOG study even if they do not allow their blood to be collected and used for this research study and/or for future research. Women already enrolled on GOG-0213 will need to be re-consented for this collection.

2.12 Single Nucleotide Polymorphisms (SNPs) and SNP Profiling**(06/22/09)**

It is well known that individual single nucleotide polymorphisms (SNPs) and SNP profiles are associated with many clinical aspects of cancer. This includes risk of developing invasive cancer, risk of recurrence of cancer, patient survival and chemotherapy toxicity. We propose to use genome wide SNP-association studies and individual SNP analyses to identify SNPs which correlate with a variety of clinical measures including but not limited to patient survival, recurrence of disease, response, and toxicity

2.13 Rationale for the inclusion of fallopian tube carcinoma (FTCA)

Primary carcinoma of the fallopian tube is among the rarest malignancies of the female genital tract accounting for approximately 3.3/1,000,000 women annually. Despite its rarity, the disease shares many features of ovarian and primary peritoneal cancer including, risk factors (age and nulliparity), genomic alterations (LOH 3q and 8q, 1q, 5p, 7q, 12p and 20q), genetic abnormalities (Her 2-neu, P53, and k-ras mutations), natural history (local followed peritoneal metastases), response to chemotherapy, and anticipated survival by stage.[66-68] The latter feature is modeled after primary ovarian cancer as well. Most strikingly though is the relationship between BRCA mutation and the attendant increased risk of fallopian tube cancer over baseline. A life-time risk increase of 120 fold over background has been reported for women who harbor BRCA mutation. In fact, women diagnosed with FTCA may be at greater risk for harboring a BRCA mutation than women diagnosed with ovarian cancer. As such, women undergoing risk-reducing bilateral salpingo-oophorectomy (RRBSO) are recommended to have as much of the fallopian tube resected as possible and undergo step-sectioning as is performed for the ovary.

Since there appears to be a common set of environmental and genetic risk factors for FTCA and ovarian cancer, it is not surprising that the clinical approach for these two neoplasms is similar including primary surgical resection and debulking or staging, adjuvant platinum- and taxane-based chemotherapy and surveillance protocols (including CA-125). Based on these features and the lack of consensus as to the precise diagnostic criteria separating primary entities of the ovary, fallopian tube and peritoneum it is appropriate to consider FTCA within this spectrum of disease.

## 2.14 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and peritoneal primary cancer population treated by participating institutions.

## 3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

### 3.1 Eligible Patients

3.10 Patients enrolled after August 28, 2011 must be candidates for cytoreductive surgery and consent to have their surgical treatment determined by randomization.**(08/29/11)(12/19/11)**

3.11 Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent.

3.12 Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

3.13 Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles).**(08/04/08)**

3.131 A complete response to front-line chemotherapy must include: negative physical exam, negative pelvic exam and normalization of CA125, if elevated at baseline. Although not required, any radiographic assessment of disease status (e.g. CT, MRI, PET/CT, etc) obtained following the completion of primary therapy (defined in 3.133) should be considered negative for disease.

3.132 All patients must have also had a treatment-free interval without clinical evidence of progressive disease of at least 6 months from completion of front-line chemotherapy (both platinum and taxane). Front-line therapy may have included a biologic agent (i.e. bevacizumab).

3.133 Front-line treatment may include maintenance therapy following complete clinical or pathological response. However, maintenance cytotoxic chemotherapy must be discontinued for a minimum of 6 months prior to documentation of recurrent disease. Patients receiving maintenance biological therapy **or hormonal therapy** are ELIGIBLE provided their recurrence is documented more than 6 months from primary cytotoxic chemotherapy completion (includes maintenance chemotherapy) AND a minimum 4 weeks has elapsed since their last infusion of biological therapy.**(06/22/09)**

3.14 Patients must have clinically evident recurrent disease for the purpose of this study,**(08/29/11)**

3.142*Measurable disease*(RECIST) is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be more than or equal to 20 mm when measured by conventional techniques, MRI or CT, or more than or equal to 10 mm when measured by spiral CT.

3.15 Patients must have adequate:

3.151 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/$mm^3$, equivalent to Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) Grade1.

3.152 Platelets greater than or equal to 100,000/$mm^3$. (CTCAE Grade 0-1).

3.153 Renal function: Creatinine (non-IDMS) ≤ 1.5 x institutional upper limit normal (ULN), CTCAE Grade 1 **(03/15/10) (08/23/10)**

3.154 Hepatic function:

3.1541 Total bilirubin ≤ 1.5 ULN (CTCAE Grade 1).

3.1542 SGOT/AST and Alkaline Phosphatase ≤ 2.5 times the upper limit of normal in the absence of liver metastasis. SGOT/AST and Alkaline Phosphatase <5.0 times ULN in the presence of liver metastasis.

3.155 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.**

Patients must have a urine protein-to-creatinine ratio (UPCR) < 1.0 mg/dL. The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hr urine collection. Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24-hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24 hour urine). Send the sample to the lab with a request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as: protein concentration (mg/dL) / creatinine concentration (mg/dL).

3.16 (This eligibility criterion does not apply to patients enrolled after August 28, 2011).**(08/29/11)(12/19/11)**Patients who are not candidates for surgical cytoreduction are eligible for the chemotherapy randomization. Patients are not considered candidates for surgical cytoreduction if complete cytoreduction in the estimation of the investigator is impossible or a medical infirmity precludes exploration and debulking.

3.17 Patients must have met the pre-entry requirements specified in Section 7.0.

3.18 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.19 Patients must have a GOG Performance Status of 0, 1, or 2.

3.110 Patients must be at least 18 years old.

3.2 Ineligible Patients

3.21 Patients who have received more than one previous regimen of chemotherapy (maintenance is not considered a second regimen).

3.22 Patients receiving concurrent immunotherapy, or radiotherapy.

3.23 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

3.24 Patients whom have already undergone secondary cytoreduction for recurrent disease are excluded.**(08/29/11)**

3.25 Patients with a prior histologic diagnosis of borderline, low malignant potential (grade 0) epithelial carcinoma that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian or peritoneal primary cancer are eligible provided that they meet the criteria listed in Section 3.12.

3.26 Patients who require parenteral hydration or nutrition and have evidence of partial bowel obstruction or perforation.

3.27 Patients who have received prior chemotherapy for any abdominal or pelvic tumor (other than ovarian, fallopian tube, and primary peritoneal) are excluded. **(06/22/09) (03/15/10)**

3.28 Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: Stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly

differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

3.29 Patients with uncontrolled infection.

3.30 Patients with concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy.

3.31 Patients with ≥ grade 2 peripheral neuropathy

3.32 Patients with a history of allergic reactions to carboplatin and/or paclitaxel or chemically similar compounds. Patients with allergic (hypersensitivity) reactions to these chemotherapeutic agents are **NOT** excluded **IF** they were successfully retreated following a desensitization program or protocol.

3.33 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

3.34 Patients of childbearing potential, not practicing adequate contraception, patients who are pregnant or patients who are nursing are not eligible for this trial. To date, no fetal studies in animal or humans have been performed. The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for the formation of new blood vessels during development, and antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. In addition, there are unknown immediate and long-term consequences of chemotherapy administration to these women. In addition, surgical exploration as mandated by randomization during pregnancy may cause imminent mortal consequences. Further, it is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Subjects will be apprised of the large potential risk to a developing fetus.

3.35 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.36 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with active bleeding or pathologic conditions that carry high risk of bleeding such as a known bleeding disorder, coagulopathy, or tumor involving major vessels.

3.37 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with a history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases or a history of stroke within 5 years of the first date of treatment on this study.

3.38 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab. (10/01/12)**

Patients with clinically significant cardiovascular disease. This includes:

3.381 Patients with significant cardiac conduction abnormalities, i.e. PR interval > 0.24 sec or 2nd or 3rd degree AV block.

3.382 Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg.

3.383 Myocardial infarction, cardiac arrhythmia or unstable angina < 6 months prior to registration.

3.384 New York Heart Association (NYHA) Grade II or greater congestive heart failure.

3.385 Serious cardiac arrhythmia requiring medication.

3.386 Grade II or greater peripheral vascular disease (exception: episodes of ischemia < 24 hrs in duration, that are managed non-surgically and without permanent deficit).**(03/15/10)**

3.387 History of CVA within six months.

3.39 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients who have had a major surgical procedure, open biopsy, dental extractions or other dental surgery/procedure that results in an open wound, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.

3.391 Patients undergoing pre-treatment secondary cytoreduction will undergo therapy with bevacizumab on cycle #2 (See Section 5.234).

3.392 Patients undergoing pre-treatment surgery for purposes other than cytoreduction may also participate provided they meet eligibility in Section 3.1. Patients randomized to arms containing bevacizumab must wait a minimum of 28 days since that procedure to begin protocol treatment. Patients who undergo an uncomplicated port placement must wait a minimum of 7 days to begin protocol treatment. **(03/15/10)**

## 4.0 STUDY MODALITIES

### 4.1 Carboplatin (Paraplatin®, NSC # 241240)

4.11 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

4.12 Solution Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

| Vial Strength | Diluent Volume |
|---|---|
| 50 mg | 5 ml |
| 150 mg | 15 ml |
| 450 mg | 45 ml |

These dilutions all produce a carboplatin concentration of 10 mg/ml.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

4.13 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.14 Stability: When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

4.15 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.16 Administration: See Section 5.2.

4.17 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation
Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms
Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance

Hepatic: Abnormal liver function tests including bilirubin, SGOT, and alkaline phosphatase
Electrolyte Changes: Abnormally decreased serum electrolyte values reported for sodium, potassium, calcium, and magnesium.
Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.

Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.
Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic-uremic syndrome has been reported rarely. Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.2 Paclitaxel (Taxol®, NSC #673089)

4.21 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300 mg vials.

4.22 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 ml is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-

II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.23 Storage: The intact vials can be stored in a temperature range between 2-25° C (36-77°F).

4.24 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

4.25 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.26 Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. See section 5.2.

4.27 Adverse Effects: Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, injection-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches

Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

4.3 Bevacizumab (NSC #704865, IND #113912) **(08/04/08) (12/19/11)**

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

4.31 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

4.32 How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in a 400 mg (25mg/ml – 16 mL) fill

glass vial containing bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

4.33 Storage and Stability: Bevacizumab is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2$^{o}$ to 8$^{o}$C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

4.34 Preparation: Vials contain no preservative and are intended for single use only. Place the calculated dose in 100 mL of 0.9% Sodium Chloride for injection. Once diluted in 0.9% Sodium Chloride for injection, the bevacizumab solution must be administered within 8 hours.

4.35 Administration: Bevacizumab is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all

subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:
1. When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.
Please note: the flush is not included in the total recommended infusion times.

### 4.36 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC #704865) **(08/23/10) (12/19/11) (09/29/14)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, August 1, 2013**[1]

| **Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 3)*** |
| | | Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy) | |
| | Febrile neutropenia | | ***Febrile neutropenia (Gr 3)*** |
| CARDIAC DISORDERS | | | |
| | | Acute coronary syndrome[2] | |

| | | | |
|---|---|---|---|
| | Cardiac disorders - Other (supraventricular arrhythmias)[3] | | ***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)*** |
| | | Heart failure | |
| | | Left ventricular systolic dysfunction | |
| | | Myocardial infarction[2] | |
| | | Ventricular arrhythmia | |
| | | Ventricular fibrillation | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 3)*** |
| | Colitis | | ***Colitis (Gr 3)*** |
| | Constipation | | ***Constipation (Gr 3)*** |
| | Diarrhea | | ***Diarrhea (Gr 3)*** |
| | Dyspepsia | | ***Dyspepsia (Gr 2)*** |
| | | Gastrointestinal fistula[4] | |
| | Gastrointestinal hemorrhage[5] | | ***Gastrointestinal hemorrhage[5] (Gr 2)*** |
| | Gastrointestinal obstruction[6] | | |
| | | Gastrointestinal perforation[7] | |
| | | Gastrointestinal ulcer[8] | |
| | Ileus | | |
| | Mucositis oral | | ***Mucositis oral (Gr 3)*** |
| | Nausea | | ***Nausea (Gr 3)*** |
| | Vomiting | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Fatigue | | ***Fatigue (Gr 3)*** |
| | Infusion related reaction | | ***Infusion related reaction (Gr 2)*** |
| | Non-cardiac chest pain | | ***Non-cardiac chest pain (Gr 3)*** |
| | Pain | | ***Pain (Gr 3)*** |
| IMMUNE SYSTEM DISORDERS | | | |
| | Allergic reaction | | ***Allergic reaction (Gr 2)*** |
| | | Anaphylaxis | |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[9] | | ***Infection[9] (Gr 3)*** |
| | | Infections and infestations - Other (necrotizing fasciitis) | |
| | Infections and infestations - Other (peri-rectal abscess) | | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Injury, poisoning and procedural complications – Other (anastomotic leak)[10] | |
| | Wound complication | | ***Wound complication (Gr 2)*** |
| | Wound dehiscence | | ***Wound dehiscence (Gr 2)*** |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 3)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 3)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 3)*** |
| | Blood bilirubin increased | | ***Blood bilirubin increased (Gr 2)*** |
| | Cardiac troponin I increased | | |
| Neutrophil count decreased | | | ***Neutrophil count decreased (Gr 3)*** |
| | Platelet count decreased | | ***Platelet count decreased (Gr 4)*** |

| | | | |
|---|---|---|---|
| | Weight loss | | ***Weight loss (Gr 3)*** |
| | White blood cell decreased | | ***White blood cell decreased (Gr 3)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 3)*** |
| | Dehydration | | ***Dehydration (Gr 3)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 3)*** |
| | Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11] | | |
| | Myalgia | | ***Myalgia (Gr 3)*** |
| | Osteonecrosis of jaw[12] | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | ***Dizziness (Gr 2)*** |
| | Headache | | ***Headache (Gr 3)*** |
| | | Intracranial hemorrhage | |
| | | Ischemia cerebrovascular[2] | |
| | Peripheral sensory neuropathy[13] | | |
| | | Reversible posterior leukoencephalopathy syndrome | |
| | Syncope | | |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| | Hematuria | | ***Hematuria (Gr 3)*** |
| | Proteinuria | | ***Proteinuria (Gr 2)*** |
| | | Renal and urinary disorders - Other (Nephrotic Syndrome) | |
| | | Urinary fistula | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| Reproductive system and breast disorders - Other (ovarian failure)[14] | | | |
| | | Vaginal fistula | |
| | Vaginal hemorrhage | | ***Vaginal hemorrhage (Gr 3)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Allergic rhinitis | | ***Allergic rhinitis (Gr 3)*** |
| | | Bronchopleural fistula | |
| | | Bronchopulmonary hemorrhage | |
| | Cough | | ***Cough (Gr 3)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |
| | Epistaxis | | ***Epistaxis (Gr 3)*** |
| | Hoarseness | | ***Hoarseness (Gr 3)*** |
| | | Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) | |
| | | Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Pruritus | | ***Pruritus (Gr 2)*** |
| | Rash maculo-papular | | ***Rash maculo-papular (Gr 2)*** |

| | | | |
|---|---|---|---|
| | Urticaria | | ***Urticaria (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| Hypertension | | | ***Hypertension (Gr 3)*** |
| | Thromboembolic event | | ***Thromboembolic event (Gr 3)*** |
| | | Vascular disorders - Other (arterial thromboembolic event)[2,15] | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak

[11]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[12]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[13]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

*[14]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of*

*menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.*

[15]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.

**Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
**CARDIAC DISORDERS** - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
**EAR AND LABYRINTH DISORDERS** - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism
**EYE DISORDERS** - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
**GASTROINTESTINAL DISORDERS** - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis;Typhlitis
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (aseptic meningitis)
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction

**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
**RENAL AND URINARY DISORDERS** - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
**VASCULAR DISORDERS** - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

**Note**: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

4.37 General Information on Adverse Effects of Bevacizumab **(06/22/09)**

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR)in NCI-CTCAE v3.0 terms is included above. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.[97] In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC

(AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[98] In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or co-morbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In

phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL ± bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity**:** As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), or similar leukoencephalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical finding are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter. In RPLS associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. RPLS/ PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is the key to diagnosis. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the

offending drug, is important in order to prevent irreversible tissue damage.**(06/22/09)**

Neutropenia: when combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab arm + IFL vs 14% in the IFL arm (grade 4 neutropenia was 3% vs 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs 17%), febrile neutropenia (5.4% vs 1.8%), and an increased risk of infection with neutropenia (4.4% vs 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs none in the chemotherapy control arm.**(06/22/09)**

4.38 Agent Ordering and Agent Accountability**(08/04/08)**

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

4.39 Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

4.40 Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)**(6/22/09)**

4.4 Docetaxel (Taxotere® RP-56976, NSC #628503)

4.41 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

4.42 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

4.43 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.

4.44 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

4.45 Adverse Effects: Consult the package insert for the most current and complete information.

4.46 Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.5 Gemcitabine**(10/01/12)**

4.51 Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol and sodium acetate.

4.52 Gemcitabine requires dilution prior to use. The lyophilized product will be reconstituted with normal saline added to the vial in order to make a

solution ideally containing 10 mg/ml or </= 40 mg/ml for 200 mg and 1 gram vials.

4.53 Storage: Unopened vials of gemcitabine are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25ºC) and used within 24 hours.

4.54 Preparation: An appropriate amount of drug will be administered as prepared or diluted with an additional 100 ml of normal saline. Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25ºC) and used within 24 hours.

4.55 Administration: Gemcitabine will be infused over 1 hour

4.56 Adverse Effects: Consult the package insert for the most current and complete information.

4.57 Supplier: Commercially available from Eli Lilly Pharmaceuticals. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.6 Pathology Requirements **(6/22/09)**

4.61 Eligible Patients: Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent. Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

4.62 Ineligible Patients: Patients with a gynecologic malignancy other then epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma.

4.63 Requirements and Instructions: Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. See section 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports and forms.

## 5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient entries will be accepted, an official signed CTSU IRB Certification Form and a CTSU IRB/Regulatory Approval Transmittal Sheet (forms can be downloaded at **www.ctsu.org**) must be received by the CTSU Regulatory Office. These forms can be faxed or mailed to:

**CTSU Regulatory Office**
**Coalition of National Cancer Cooperative Groups**
**1818 Market Street, Suite 1100**
**Philadelphia, PA 19103**
**1-888-823-5923**
**FAX 215-569-0206**

### 5.1 Patient Entry and Registration **(09/29/14)**

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at on the GOG web menu page and clicking on the OPEN link.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan **(06/22/09)**

5.21 Patients meeting eligibility requirements will be considered first for the surgical randomization aspect of the trial. Suitability for secondary cytoreduction will be made by the individual patient's Attending Physician. Guidelines for consideration in assessing candidacy for secondary cytoreduction are listed in Section 5.211. If the patient is considered to be a suitable surgical candidate she will undergo randomization as outlined in Section 5.22.

(The following two sentences do not apply to patients enrolled onto the study after August 28, 2011): If the patient is considered not to be a suitable surgical candidate she will be allowed to participate in the chemotherapy randomization aspect of the trial as outlined in Section 5.23. Patients undergoing surgical randomization will also be randomized to a chemotherapy regimen at the same time. **(08/29/11)(12/19/11)**

5.211 Guidelines for Secondary Cytoreduction: The goal of secondary cytoreduction is **COMPLETE REMOVAL OF ALL VISIBLE DISEASE**. While no specific eligibility can be globally provided, patients with recurrent disease which will not be addressed at surgery should not undergo surgical randomization. In general, women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction. Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc) are poor candidates, if the disease is felt unresectable by preoperative evaluation. Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT). Although it is recognized that patients with longer treatment-free intervals may be considered better surgical candidates (providing some expansion of the preoperative tumor volume characteristics) than those with shorter treatment-free intervals, the primary tenet of surgery for this study in all women enrolled in this arm is complete surgical resection (no visible residual).

5.22 Randomization I: ***Surgery***: Patients entered onto the surgical arm of the trial will undergo abdominal exploration with cytoreduction as outlined in (Appendix II) within 4 weeks of registration. Chemotherapy will be administered following recovery up to 6 weeks after surgery. A discussion with the study chair is required if study treatment is not initiated within 6 weeks of surgery.**(6/22/09) (03/15/10)**

5.23 Randomization II: ***Chemotherapy*****. (Between Dec 6, 2007 and August 28, 2011 the following 4 treatment arms were randomly assigned to**

**patients enrolled into this study. Beginning August 29, 2011 all patients are required to be surgical candidates, and only the surgical component of treatment is randomized. For these later patients the systemic treatment, which consists of either paclitaxel+carboplatin (as described for arms I and III) or gemcitabine+carboplatin (as described for arms V and VII) or paclitaxel+carboplatin+bevacizumab (as described for arms II and IV) or gemcitabine+carboplatin+bevacizumab (as described for arms VI and VIII) is selected and declared prior to enrolling onto the study. (08/29/11)(12/19/11) (10/01/12)**

**Patient chooses systemic treatment with either:**
**a) carboplatin + paclitaxel or gemcitabine or**
**b) carboplatin + paclitaxel or gemcitabine + bevacizumab**

5.231 Regimens: **(06/22/09) (03/15/10) (10/01/12)**

| Arm | Surgery | Chemotherapy* | Schedule | Maintenance Regimen |
|---|---|---|---|---|
| **I** | No | Paclitaxel 175 mg/m$^2$ ** Carboplatin AUC 5 | Every 21 days (Section 5.24) | None |
| **II** | No | Paclitaxel 175 mg/m$^2$ ** Bevacizumab 15 mg/kg Carboplatin AUC 5 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |
| **V** | No | Gemcitabine 1000 mg/m$^2$ d1 & d8 Carboplatin AUC 4 day 1 | Every 21 days (Section 5.24) | None |
| **VI** | No | Gemcitabine 1000 mg/m$^2$ d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |
| **III** | Yes | Paclitaxel 175 mg/m$^2$ ** Carboplatin AUC 5 | Every 21 days (Section 5.24) | None |
| **IV** | Yes | Paclitaxel 175 mg/m$^2$ ** Bevacizumab 15 mg/kg Carboplatin AUC 5 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |

| | | | | |
|---|---|---|---|---|
| **VII** | Yes | Gemcitabine 1000 mg/m$^2$ d1 & d8 Carboplatin AUC 4 day 1 | Every 21 days (Section 5.24) | None |
| **VIII** | Yes | Gemcitabine 1000 mg/m$^2$ d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |

*All chemotherapy doses on day one unless otherwise indicated. For those patients randomized to cytoreductive surgery, bevacizumab is to be started at the 2$^{nd}$ cycle of therapy.
** Note: docetaxel 75mg/m$^2$ IV over 1 hour may be substituted for paclitaxel (see Sections 5.233and 6.161).

5.232 Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

5.233 Sequence and timing of drug administration: **(08/04/08) (03/15/10)(08/29/11)(12/19/11)(10/01/12)**

- **Paclitaxel** will be infused over 3 hours. (Note, for circumstances in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m$^2$ see Sections 6.161 and 6.167).
- **Bevacizumab** administration will be as a short intravenous infusion following paclitaxel infusion. Anaphylaxis precautions should be observed during bevacizumab administration. The initial dose would be administered over 90 ± 15 minutes. If no adverse reactions (including fever and or chill) occur, the second dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.
- **Bevacizumab has been associated with an increase in wound complications and bowel perforations in post-operative patients. Thus, patients in Randomization I who undergo surgery and are to receive bevacizumab after Randomization II will have the first cycle of therapy without bevacizumab. They will receive it in cycle #2.**
- **Gemcitabine will be administered over 60 minutes on days 1 and 8 of each 21-day cycle. Patients will be monitored prior to each dose with a complete blood count, including differential counts.**

- **Carboplatin** will be administered as a 60-minute infusion. When administered in conjunction with other medications, carboplatin will be infused after the other agents. Carboplatin, either alone or in combination should be premedicated with dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.234 Pre-Medication:**(10/01/12)**

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

When carboplatin and paclitaxel are administered with bevacizumab, it is recommended that the preparatory regimen as outlined above should be given 30 minutes if IV or 60 minutes if PO before infusion to reduce the risk of hypersensitivity associated with these agents.

In the event of a prior bevacizumab hypersensitivity reaction the prophylactic regimen should be repeated prior to subsequent doses of bevacizumab (Section 5.2551). Thus, the patient will be premedicated prior to paclitaxel AND prior to bevacizumab.

For all courses where docetaxel is to be administered, (see Sections 6.161 and 6.167) it is recommended that patients be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate $H_1$ blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

5.235 Antiemetic Regimens**(10/01/12)**
It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,

- Granisetron 1 mg IV (or 2 mg PO) 30 minutes prior to chemotherapy plus dexamethasone 10 mg IV, with or without lorazepam 0.5 – 2.0 mg IV 30 minutes prior to chemotherapy.
- Be sure to give prescription(s) for prevention of delayed nausea/vomiting as per institutional guidelines/standards.

5.236 Dosing of Paclitaxel **(06/22/09)**

The initial dose of paclitaxel will be 175 mg/m$^2$. Alterations in this dose are presented in Section 6.1612. As such, patients whose body weight changes by 10% or more should undergo recalculation based on the adjusted body surface area.

5.237 Dosing of bevacizumab **(06/22/09)(08/29/11)**

Bevacizumab will be administered at 15 mg/kg IV. **For patients randomized to the chemotherapy arm, the** weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. For patients undergoing the second surgical procedure **the** baseline weight for calculating the bevacizumab dose should be post-op. If a patient's weight changes by ≥ 10% during the course of the study, the bevacizumab dose will be recalculated.

5.2371 Supportive Care Guidelines for Bevacizumab

If an infusion-related adverse reaction occurs, the patient should be pre-medicated prior to subsequent doses of bevacizumab (Section 5.234); however, the infusion time for bevacizumab may not be decreased for the next infusion. If a patient experiences an infusion-associated averse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes ± 15 minutes.

5.238 Dosing of Carboplatin **(03/15/10) (08/23/10) (1/3/11)**

**See Appendix V for current Carboplatin dose calculation instructions**

**5.239 Dosing of Gemcitabine (10/01/12)**
**See Section 5.233**

5.24 Duration of treatment – Paclitaxel or Gemcitabine and Carboplatin (Arm I, Arm III, Arm V, and Arm VII): **(06/22/09)**

5.241 Patients with measurable disease achieving clinical complete response (negative physical exam, negative CT scan or MRI and normal CA-125) (CR; Section 8.131) during the chemotherapy phase will be treated with a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles), whichever is greater.

5.242 If stable or partial regression is the maximum documented response, patients will continue their chemotherapy to a maximum of 8 cycles (see Section 8.15) or adverse effects (see Section 6.0). Patients will then be

followed off therapy until documented progression occurs. (See Section 8.14) **(08/04/08)(6/22/09)**

5.243 If progressive disease is observed while on therapy, patients will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.244 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue therapy for 6 cycles or if CA-125
normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable lesions) will have chemotherapy stopped after six cycles. .

5.25 Duration of treatment – Carboplatin, Bevacizumab and Paclitaxel or Gemcitabine (Arm II Arm IV, Arm VI, and Arm VIII) **(06/22/09) (03/15/10)(10/01/12)**

5.251 Patients with measurable disease achieving clinical complete response (CR; Section 8.131) during the chemotherapy phase will be treated for a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles) and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.

5.252 If stable or partial regression is the maximum documented response, patients will receive up to 8 cycles (minimum of 6 cycles) of therapy and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.**(08/04/08)**

5.253 If progressive disease is observed while on therapy, patients in all arms will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.254 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue chemotherapy and the biologic agent for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.15); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable disease) will have chemotherapy stopped after six cycles. The maintenance regimen will begin after completing chemotherapy and continue until progression or adverse effects preclude additional treatment.

5.26 Biometric considerations in dose calculation

Maximum body surface area used for dose calculations will be 2.0 $m^2$ as per GOG Chemotherapy Procedures Manual

5.3 Secondary Cytoreduction: **(06/22/09)**

The value of secondary surgical cytoreduction is being evaluated in this trial through a randomization of surgical candidates deemed appropriate by their treating physicians. Participation in the surgical randomization arm of this trial is **NOT** required for entry on this study. Patients with recurrent disease, meeting entry criteria but deemed not appropriate for surgical exploration are eligible to participate in the chemotherapy randomization. Those patients for whom their treating physicians consider appropriate for surgery will be randomized to either secondary cytoreduction or no surgery prior to a second randomization of chemotherapy. Surgical exploration should be undertaken within 28 days of registration onto this study.

5.31 Procedures and goals of secondary cytoreduction are outlined in Appendix II.

5.32 Please see Section 7.3 for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix III for a detailed description of the Specimen Procedures for GOG-0213.

## 6.0 TREATMENT MODIFICATIONS

### 6.1 Dose Modifications:

Since chemotherapy in the recurrent setting is largely palliative, infusion without routine use of growth factor support will be attempted. Certain chemotherapy combinations have additive hematologic toxicity and other combinations are characterized by differing hematologic toxicity. Therefore, dose modification will be based on dose-limiting toxicity (DLT) for either or both neutropenia (ANC) or thrombocytopenia (PLT) and conducted as outlined in the following table below.

If a dose reduction is indicated, recalculate chemotherapy dosages using the baseline weight and serum creatinine. **(03/15/10)**

6.11 Dose-limiting neutropenia (DLT-ANC) is defined as:

- Febrile neutropenia: febrile is defined as fever ≥ 38.5°C, with or without documented infection in the presence of an ANC of 1000 cells/$mm^3$ or less
- Prolonged Grade IV ANC persisting ≥ 7 days.
- Uncomplicated Grade IV ANC, < 7 days, is NOT a DLT.

6.12 Dose-limiting thrombocytopenia (DLT-PLT) is defined as:

- Grade IV thrombocytopenia (< 25,000/$mm^3$)
- Grade III thrombocytopenia (25,000 to 50,000/$mm^3$) complicated by bleeding, easy bruising, petechiae or requiring platelet transfusion (see Section 6.141)
- Uncomplicated Grade III thrombocytopenia is NOT a DLT

6.13 Guidelines for dose modification based on dose-limiting neutropenia and thrombocytopenia: (nadirs)

**Table A**

| DLT ANC‡ | DLT PLT§ | First Occurrence | Second Occurrence | Third Occurrence |
|---|---|---|---|---|
| Yes | No | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Add myeloid growth factor **AND** maintain all drug doses | Off Study Treatment, Follow-up Continued |
| Yes | Yes | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Off Study Treatment, Follow-up Continued | |
| No | Yes | Decrease one AUC unit **AND** maintain other drug doses * | Off Study Treatment, Follow-up Continued | |

‡ DLT-ANC: Neutropenic Dose-Limiting Toxicity (Section 6.11)

§ DLT-PLT: Thrombocytopenic Dose-Limiting Toxicity (Section 6.12)

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167, dose modifications can be found in Table B-2.

6.14 Adjustments for Hematologic Toxicity **(03/15/10)**

6.141 **Hemorrhage**: Patients receiving bevacizumab who develop a CTCAE V3.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V3.0

Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met (continue carboplatin and paclitaxel):

- bleeding has resolved
- blood hemoglobin level is stable (serial measures with less than 10% change)
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence.

Patients who experience delay of resolution according to the above criteria for greater than 3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE V3.0 Grade 4 hemorrhage will be taken off study treatment.

6.142 **Thrombosis:(03/15/10)**

Arterial Thrombosis
Patients will be taken off study treatment for ≥ CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

Venous Thrombosis
All therapy (carboplatin, paclitaxel, and bevacizumab)will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. If the planned duration of full-dose anticoagulation is ≤ 3 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 3 weeks, treatment may be resumed

during the period of full dose anticoagulation if ALL of the following criteria are met (otherwise the patient will be taken off study treatment):

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.
- The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The subject must not have had hemorrhagic events while on study.
- The patient is benefiting from treatment (no evidence of disease progression).

Patients with symptomatic CTCAE Grade 4, or recurrent/worsening thromboembolic events after resumption of bevacizumab, will be taken off study treatment.

6.143 **Coagulopathy**: For CTCAE V3.0 Grade 3 or 4 coagulopathy: hold all therapy (carboplatin, paclitaxel, and bevacizumab), until PT resolves to Grade 1. For patients with PT/INR > therapeutic range while on therapeutic warfarin, hold treatment until PT/INR within therapeutic range. Patients experiencing treatment delay >3 weeks because of failure to meet the above criteria will be taken off study. **(06/22/09) (03/15/10)**

**Table B-1 Regimen modifications for DLTs (6.11-613), hematologic toxicities (6.141-6.143) and delayed hematologic toxicity (6.153)(03/15/10)**

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I and III | Paclitaxel * | 135 mg/m$^2$ | 175 mg/m$^2$ |
| | Carboplatin | AUC 4 | AUC 5 |
| II and IV | Paclitaxel * | 135 mg/m$^2$ | 175 mg/m$^2$ |
| | Bevacizumab | 15 mg/kg | 15 mg/kg |
| | Carboplatin | AUC 4 | AUC 5 |

* See Table B-2 below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

**Table B-2 Dose Levels for Docetaxel***

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I-IV | Docetaxel | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.15 General Guidelines for **Delayed Hematologic Toxicity**

6.151 No subsequent chemotherapy cycle shall begin until the absolute neutrophil count (ANC) ≥ 1,500/mcl and platelets ≥ 100,000/mcl. No subsequent cycle of maintenance bevacizumab shall begin until the ANC is ≥ 1000/mcl and platelets are ≥ 75,000/mcl. **(03/15/10)**

6.152 Failure of the counts to recover appropriately by day 21 will require delay of the subsequent treatment until adequate count recovery.

6.153 Patients who require a delay of greater than 1 but ≤ 2 weeks for adequate count recovery (with or without growth factors) will have subsequent treatment with a one level dose reduction. Patients who have a second delay of greater than 7 days will require the use of myeloid growth factors in all subsequent cycles. Patients who have a delay of > 2 weeks will have a one level dose reduction and the addition of myeloid growth factors in all subsequent cycles. **(03/15/10)**

6.154 Patients who require a delay of greater than 3 weeks for adequate count recovery (with or without growth factors) will be removed from study treatment, but follow-up will continue.

6.155 There will be no dose modification on the basis of uncomplicated WBC or ANC nadirs.

6.156 Patients will NOT receive prophylactic thrombopoietic agents on this study.

6.1561 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

6.1562 Patients may not receive amifostine or other protective reagents, unless indicated in the study design.

6.16 Adjustments for Non-hematologic Toxicity

Individual agents may be associated with specific non-hematological toxicity which warrants dose modification. Allowable dosing modifications are presented in the following table:

**Table C Regimen modifications for non-hematologic toxicities (see dose adjustments per toxicity type as outlined below**

| Agent | -2 Level | -1 Level | Starting Dose Level |
|---|---|---|---|
| Carboplatin | Off study treatment | AUC 4 | AUC 5 |
| Paclitaxel | 110 mg/m$^2$ | 135 mg/m$^2$ | 175 mg/m$^2$ |
| Bevacizumab | Off study treatment | 15 mg/kg | 15 mg/kg |
| Docetaxel * | 55 mg/m$^2$ | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.161 **Neurologic toxicity:** Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in subsequent therapy (all agents) for a maximum of 3 weeks until recovered to grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due then paclitaxel should be withheld from all subsequent chemotherapy cycles. For patients with persistent Grade 2 neurotoxicity, substitute docetaxel, unless medically contraindicated, according to Section 5.233.**(03/15/10)** Patients with persistent Grade 3-4 neurotoxicity should be removed from study.

In such cases where docetaxel has been substituted for paclitaxel, if CTCAE Grade 3 or 4 peripheral neuropathy occurs during or after the first cycle of docetaxel substitution then subsequent doses of docetaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade ≤ 2. If peripheral neuropathy fails to recover to Grade ≤ 2 by a maximum delay of three weeks from time therapy is due, then the patient is removed from study. **(08/23/10)**

6.162 **Gastrointestinal toxicity:** There will be no dose modifications for nausea, diarrhea, or constipation. It is recommended that routine medical measures be employed to manage nausea and constipation.

6.163 **Renal toxicity:** If renal function worsens on therapy, an investigation for underlying causes should be undertaken. Calculated or measured creatinine clearance under 40 ml/min or significant worsening of the renal function (50% reduction in calculated CrCl) requires withholding treatment until a cause is identified or renal function improves. In particular, disease progression should be ruled out. In these patients creatinine clearance should be evaluated weekly. If calculated or measured CrCl is less than 40 ml/min after a two-week delay, the Study Chair must be notified. No treatment is to be given to a patient with a calculated or measured CrCl less than 40 ml/min.

6.164 **Proteinuria:(06/22/09)** Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.

UPC ratio ≤ 3.5 (CTCAE, v3.0 Grade 0-2) Continue bevacizumab. UPC ratio > 3.5 hold bevacizumab until UPC ratio recovers to ≤3.5. If bevacizumab is held for > 3 weeks, the patient is removed from study. Grade 4 or nephrotic syndrome: Patient is removed from study.
*** Please note chemotherapy may be administered if bevacizumab is held for Grade 3 proteinuria.**

6.165 **Hepatic toxicity:** Hepatic toxicity is not expected as a direct complication of chemotherapy in this population using the prescribed dose and schedule for each regimen. However, the development of grade 3 (or greater) elevations in SGOT (AST), alkaline phosphatase or bilirubin requires reduction of one dose level in all study drugs with the exception of carboplatin and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If therapy is held for > 3 weeks the patient is removed from study.

6.166 There will be no dose modifications for alopecia.

6.167 **Hypersensitivity reaction to paclitaxel or bevacizumab:** The occurrence of a hypersensitivity reaction to paclitaxel or bevacizumab is **not** considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication (such as decadron 20 mg IV and diphenhydramine 50 mg IV 30 minutes prior to reinfusion) to prevent hypersensitivity reaction and may utilize a slow initial infusion rate of the suspected agent which is gradually increased to the standard infusion rate in the absence of reaction (such as 1 cc of the original IV solution diluted in 100 ml over 10 minutes, then 5 cc in 100 ml over 10 minutes then 10 cc in 100 ml over 10 minutes and finally, the original solution at the original speed). However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusional reactions to bevacizumab, the patient is removed from study. In the event of recurrent hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel, according to guidelines in Sections 5.233 and 6.161.

**Hypersensitivity reaction to carboplatin**: The occurrence of a hypersensitivity reaction to carboplatin may occur in this previously treated population. Successful retreatment has been reported with a modified dilution and infusion schedule.[45,46] A suggested desensitization protocol that may be used in patients with a carboplatin hypersensitivity is reduced infusion dose of 1:1000 dilution (0.1cc in 100 ml) over 1 hour, followed by a 1:100 dilution (1.0 cc in 100 ml) over 1 hour, followed by a 1:10 dilution (10 cc in 100 ml) over 1 hour, followed by 1:1 concentration for the remaining infusion. Patients experiencing a significant hypersensitivity reaction to carboplatin may be removed at the discretion of the treating physician if it is felt to be unsafe to offer a desensitization program.**(08/29/11)**

6.168 **Hypertension**: Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab included ACE inhibitors, Beta blockers, diuretics, and calcium channel blockers.

- For controlled hypertension, defined as systolic ≤ 150 mm Hg and diastolic ≤ 90 mmHg, continue therapy;
- For uncontrolled hypertension (systolic > 150 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE V3.0 Grade 4, hold all therapy (carboplatin, paclitaxel, and bevacizumab) for one week with anti-hypertensive therapy initiated or continued. **(03/15/10)**
- If hypertension is controlled and symptomatic hypertension has resolved by three weeks after holding treatment, continue all therapy.
- If hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE V3.0 Grade 4, persists after three weeks after holding treatment, the patient is removed from study.
- Any patient developing CTCAE V3.0 Grade 4 hypertension will be removed from study.

6.169 **Wound disruption**: Patients will be removed from study in the event of a wound disruption requiring medical or surgical intervention.

6.1610 **Bowel perforation/obstruction/fistula/GI leak**: For new development of bowel perforation, bowel obstruction (partial or complete), fistula, or GI leak (any grade); the patient will be taken off study treatment.

6.1611 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs.

6.1612 **Weight loss:** If a patient's weight changes by ≥ 10% during the course of the study, the doses of paclitaxel (or docetaxel) and bevacizumab will be recalculated. For patients undergoing the second surgical procedure the baseline weight for calculating the carboplatin and bevacizumab should be the patient's postoperative weight. **(08/04/08)**

6.1613 **RPLS (Reversible Posterior Leukoencephalopathy Syndrome) or PRES (Posterior Reversible Encephalopathy Syndrome):** Hold bevacizumab in patients with symptoms/ signs suggestion of RPLS/ PRES; subsequent management should include MRI scans and control of HTN. Discontinue bevacizumab upon diagnosis of RPLS/ PRES unless the patient meets the criteria below. **(03/15/10)**

Note**: (06/22/09)**

- Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the study chair and approved by the sponsor.
- Chemotherapy may continue if the patient is considered medically stable for infusion.

6.17 No dose-escalations are allowed on this study.

**6.18 Dose modifications for Gemcitabine/carboplatin (Arms V, VI, VII, VIII) (10/01/12)**

**6.181 Carboplatin and Gemcitabine (Day1)**

Carboplatin and gemcitabine dosing on Day 1 of each cycle should be held if ANC is <1500/μL, Hgb is <8.5 g/dL, or platelets are <100,000/μL within 24 hours of the scheduled treatment. The chemotherapy can be delayed for a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate

counts(with or without growth factors) within the 3 weeks will no longer receive protocol- defined chemotherapy but will enter into the maintenance phase to receive the study drug (bevacizumab or observation) alone. Study drug can be held for up to 3 weeks if carboplatin and gemcitabine are held in order to allow for same-day administration of carboplatin and gemcitabine and study drug (if chosen).

Dose adjustment for gemcitabine in combination with carboplatin for subsequent cycles is based on toxicity observed during the preceding cycle. The dose of gemcitabine should be permanently reduced to the 800 mg/m$^2$ on Days 1 and 8, in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10$^6$/L for more than 5 days
- Absolute granulocyte count <100 x 10$^6$/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10$^6$/L
- Cycle delay of more than one week due to toxicity If any of the above toxicities recur after the initial dose reduction for the subsequent cycles, gemcitabine should be given only on day 1 at 800 mg/m$^2$ (omit gemcitabine on Day 8).

### 6.182 Gemcitabine Dose Modification within a Treatment Cycle (Day 8)

Gemcitabine dosage adjustments for hematologic toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy, as shown in the Table.

**TABLE: Day 8, Gemcitabine Dose Modification for Hematological Toxicity**

| Absolute granulocyte count (/mm$^3$) | | Platelet count (/mm$^3$) | Gemcitabine Dose |
|---|---|---|---|
| ≥ 1500 | and | ≥100,000 | 100% D1 dose |
| 1000−1499 | and/or | 75,000−99,999 | 50% D1 dose |
| <1000 | and/or | <75,000 | Omit D8 dose |

If a patient experiences an HSR, platinum desensitization may be allowed after discussion with the Study Chair. For any other dose modifications for non-hematologic toxicity, please follow institutional practice and prescribing information (also outlined in Section 6.16). In general, for severe (Grade 3 or 4) non-hematological toxicities, except nausea/vomiting, therapy with gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician. Patients who require discontinuation of either carboplatin or gemcitabine due to toxicity should continue receiving study drug with the non-discontinued chemotherapy to complete 6 cycles (7−10 cycles if deemed necessary by the investigator and approved by the Study Chair). Patients requiring discontinuation of both carboplatin and gemcitabine prior to disease progression should continue single-agent study drug until disease progression or unacceptable toxicity, as determined by the investigator.

## 7.0 STUDY PARAMETERS

### 7.1 Observations and Tests(08/04/08) (06/22/09)(03/15/10)(10/01/12)

The following observations and tests are to be performed and recorded on the appropriate form(s). **See Section 7.2 for the stained pathology slide requirements to confirm eligibility for GOG-0213 and Section 7.31 for the specimen requirements for translational research.**

| | Pre-Treatment | | During Chemotherapy Phase | | | During Maintenance/Surveillance Phase (**Patients on Arm II, IV, VI, and VIII only)** | | |
|---|---|---|---|---|---|---|---|---|
| Observations and Tests | Prior to Surgery | Prior to chemo-therapy | Weekly | Prior to Each Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Prior to Every Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Q 3 Months x 8 then q 6 Months **All Patients** |
| History & Physical | 1 | 1 | | X | | | X | |
| Blood pressure* | 1 | 1 | 2 | X | | X | X | |
| Toxicity Assessment | | | | X | | | X | |
| CBC/Differential/ Platelets | 3 | 3 | X | 4 | | 4 | | |
| Urine pregnancy test in women of child-bearing potential | 3 | | | | | | | |
| Urine Protein-Creatinine Ratio (UPCR)* | 3,5 | 3, 5 | | | 6 | | 6 | |
| Serum Creatinine | 3 | 3 | | 4 | | | 4 | |
| Bilirubin, SGOT/AST, Alkaline Phosphatase | 3 | 3 | | 4 | | | 4 | |
| Ca/PO4/Mg | | 3 | | 7 | | | 7 | |
| Serum CA-125 Level | 1 | 1 | | 4,13 | | | 4,13 | 13 |
| PT/PT INR/PTT* | 3 | 3 | | 8 | | | 8 | |
| Audiogram | | 9 | | | | | | |
| EKG | 1 | 1 | | | | | | |
| Radiographic Tumor Measurement | 1,10 | 1, 10 | | | See footnote 11c),d) | | | 11 |
| Chest X-Ray | 1,12 | 1, 12 | | | | | | |
| QOL Survey | X,14 | X, 14 | | | 14 | | 14 | 14 |
| Incision Check* | | X | 15 | | | | | |

* Required only for patients who were enrolled prior to August 29, 2011 as well as those enrolled after this date electing to receive bevacizumab.

1. Must be obtained within 28 days of first treatment. For those patients randomized to cytoreductive surgery, these observations are repeated prior to initiating chemotherapy.

2. Blood pressure should be assessed at least weekly during the first cycle of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion.
3. Must be obtained within 14 days prior to registration. For patients randomized to cytoreductive surgery, these observations are repeated within 14 days prior to initiating chemotherapy. **(06/22/09)**
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Urine protein should be assessed by UPCR (see Section 3.37 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
6. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.
7. When clinically indicated.
8. For patients on prophylactic or therapeutic anticoagulation, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin.
9. For patients with a history of hearing loss; repeat as clinically indicated.
10. An initial CT scan (with intravenous and oral contrast, unless contraindicated) or MRI (with gadolinium, unless contraindicated and fat suppression sequence) of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within28 days prior to initiating chemotherapy.**(06/22/09)** PET-CT imaging alone cannot be used to establish extent of post-operative disease residuum unless also performed with CT or MRI as described.
11. Follow-Up Radiographic Assessment of Disease (in patients with measurable and non-measurable disease). Imaging should use the same modality and encompass the same fields as in the initial pre-treatment evaluation should be repeated with the following schedule:
    a) Within 28 days of first treatment.
    b) If the patient was randomized to cytoreductive surgery, then repeat radiographic assessment within 14 days of initiating chemotherapy.
    c) **After cycle 3 (before cycle 4) of study treatment(06/22/09)**
    d) **After cycle 6 of study treatment (06/22/09)**
    e) **After cycle 8 of study treatment (03/15/10)**
    f) Every three months for two years and then every 6 months after completion of chemotherapy during the maintenance/surveillance phase.
    Imaging assessments as part of this protocol can be discontinued if disease progression is confirmed according to guidelines in section 8.14 and 8.15.. However, if disease progression is based only on rising CA-125 criteria, then radiographic imaging must be obtained within two weeks following the date CA-125 based progression was documented.**(08/29/11)**
12. Not required if CT or MRI of chest already performed at pre-treatment baseline.
13. Progression can be based upon serum CA-125, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule. **(06/22/09)**
14. See Section 7.3. QOL surveys are to be assessed for at most 6 time points:
    a) prior to surgery (for those randomized to cytoreductive surgery).
    b) prior to initiating chemotherapy.
    c) prior to cycle 3 (6 weeks after starting chemotherapy).
    d) prior to cycle 6 (15 weeks after staring chemotherapy).
    e) 6 months after starting chemotherapy.
    f) 12 months after starting chemotherapy.
15. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection may initiate therapy, but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.1512 and Adverse Events reporting in Section 10.3.

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Protocol Eligibility (**06/22/09)**

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date.

Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting stained slides, pathology reports and Form F to the GOG Statistical and Data Center. Please see section 4.6 and 10.2 for additional requirements and instructions.

7.3 Translational Research

7.31 Specimen Requirements**(08/04/08) (06/22/09)**

A total of seven specimens will be sought from each GOG-0213 patient randomized to have secondary cytoreductive surgery. Three of these will be MANDATORY and four will be HIGH-PRIORITY OPTIONAL. Please see below for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix III for a detailed description of the Specimen Procedures for GOG-0213. A copy of Form SP will need to be completed online and

submitted to the GOG Statistical and Data Center (SDC) as specified in Section 10.2.

**The collection of a whole blood for DNA extraction and single nucleotide polymorphism (SNP) analysis will apply to all women on GOG-0213 who provide consent regardless of randomization and treatment including those already enrolled on protocol. Women who are already enrolled on GOG-0213 will need to be re-consented.**

## Quick Scan Summary of the Specimen Requirements for GOG-0213.

***(See Appendix III for detailed instructions for collecting, processing, storing, packing and shipping specimens for GOG-0213.)***

| **Required Specimens (Specimen Codes)**[1] | **Form SP Label in Forms Tracking System**[2] | **Collection Time Points and Requirements** | **Deadlines and Recommendations** [2] |
|---|---|---|---|
| Archival Formalin-Fixed and Paraffin-Embedded (FFPE) Primary or Metastatic Tumor (FT01) either<br>• 1st choice: Block<br>• 2nd choice: 16 Unstained Slides | SP-FT01-0213 | Archival primary or metastatic tumor left over from a previous surgery will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213. | Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. FT01 could also be included in the dual chamber kit if available when the other specimens were ready to ship to the Bank.<br><br>Submit Form SP for FT01 to the SDC online within 8 weeks of study entry. |
| Pre-Op Serum (SB01)<br><br>Pre-Op Plasma (PB01) | SP-SB01-0213<br><br>SP-PB01-0213 | Pre-op serum and plasma will be an optional but high priority requirement for **women who consent and undergo surgery** on GOG-0213. The blood to prepare these specimens must be collected after providing consent for this research study but prior to undergoing secondary cytoreductive surgery. | Ship the FR01 and RR01 (mandatory requirement) and any of the optional specimens (SB01, PB01, FN01 and/or RN01) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible as described below [6] and in Appendix III.<br><br>Submit Form SP for each of these specimens to the SDC online within 7 days of surgery. |
| Fixed Recurrent Tumor (FR01) in a jar of formalin or embedded in a paraffin block [4]<br><br>Frozen Recurrent Tumor (RR01) snap frozen piece or frozen in OCT mold [4] | SP-FR01-0213<br><br>SP-RR01-0213 | Recurrent tumor will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen tumor will need to be removed during secondary cytoreductive surgery. | |

| | | | |
|---|---|---|---|
| Fixed Normal Tissue[4,5](FN01) in a jar of formalin or embedded in a paraffin block<br><br>Frozen Normal Tissue[4,5](RN01) snap frozen piece of frozen in OCT mold | SP-FN01-0213<br><br>SP-RN01-0213 | Normal tissue will be an optional but high priority requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen normal tissue will need to be removed during secondary cytoreductive surgery. | |
| Whole Blood (WB01)[7] to extract DNA for SNP analysis.<br>• Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA. | SP-WB01-0213 | Collect prior to or after starting treatment on this phase III trial or at any time during follow up from **all women on protocol who provide consent regardless of randomization and treatment** including women already enrolled on GOG-0213. Collect on a Monday through Friday schedule. **Do not collect this blood the day before a holiday.** | Ship WB01 to the GOG Tissue Bank at ambient temperature the day the blood is collected.[7]<br><br>Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected. |

[1] Label each specimen with the protocol number (GOG-0213), a GOG Bank ID (# # # # - # # – G # # #), a specimen code (see above) and the collection date (mm/dd/yyyy).

[2] Please complete Form SP for EACH specimen and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix III.

[3] The block or 16 unstained slides of primary tumor (FT01) must be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0213, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.Refer to Section IV and Section IX in Appendix III for important instructions for preparing and shipping the archival FFPE primary and/or metastatic tumor specimens to the GOG Tissue Bank for GOG-0213.If more than one type of fixed tumor will be submitted, please label the tumor specimens sequentially using FT01 for primary tumor tissue and FT02 for metastatic tumor, and contact the GOG Statistical and Data Center to have the optional SP Form for FT02 added to the patient form schedule. In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, not enough tumor for research, referring site won't release tumor).

[4] **Quantity of tissue needed for research: Please submit as much tissue as possible for research. Gram quantities are ideal.** Visually, one gram of tissue is about the size of five quarters stacked on top of each other (i.e., one quarter in diameter and five stacked quarters in height). Please try to submit gram quantities whenever possible. Larger amounts of tissue will allow for replicate laboratory testing to be performed and will enable multiple assays to be run on the same specimen.

[5] **Normal tissue can be any normal epithelial tissue including non-involved ovary, Fallopian tube, uterus, cervix, or skin. When normal epithelium is not available, please submit non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.** Please try to submit normal epithelium whenever possible as this type of tissue will serve as the most appropriate control for the laboratory testing to be preformed for this protocol. **Note for the pathologist,** in the unlikely event that any tumor tissue is subsequently identified within the normal tissue submitted for research, the Pathology Department at the treating institution will be informed and the material will be immediately returned for diagnostic purposes. Please try to submit as much normal tissue as possible. The larger the piece the better.

6 Ship the surgical specimens including fixed recurrent tumor (FR01) and frozen recurrent tumor and any of the optional high priority specimens (fixed normal tissue [FN01], frozen normal tissue [RN01], serum [SB01] and plasma [PB01]) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible to the GOG Tissue Bank (address provided above) with a completed SP Form for each specimen. These specimens can be shipped on a Monday through Thursday schedule for Tuesday through Friday delivery using shipping labels obtained through the GOG Tissue Bank's Kit Management application.**(08/29/11)** Refer to footnotes 4, 5 and 6 in the Quick Scan Summary of Specimen Requirements for GOG-0213 as well as Section V and Section IX in Appendix III for important instructions for preparing and shipping the surgical specimens to the GOG Tissue Bank for GOG-

0213.Refer to Section VI and Section IX in Appendix III for important instructions for preparing and shipping the frozen serum to the GOG Tissue Bank for GOG-0213. In the event that it is not possible to submit any of these specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible, tumor not present during surgery, not enough tumor or tissue for research).

[7] Whole blood specimen for GOG-0213 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. The blood must be shipped at ambient temperature the day it is collected as the blood will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank *FedEx Priority Overnight* on a Monday through Friday schedule for Tuesday through Saturday delivery using the a shipping label obtained through the GOG Tissue Bank's Kit Management application. **Do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood. Refer to Section VII and Section IX in Appendix III for important instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0213as the GOG Tissue Bank cannot provide Shipping Kits for submitting the whole blood specimen for this protocol. In the event that it is not possible to submit the whole blood specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible).

### 7.32 Creation of Tissue Microarrays (TMAs) for GOG-0213**(06/22/09)**

The GOG Tissue Bank will collaborate with the GOG Statistical and Data Center and the GOG Tissue Utilization Subcommittee to design and create a series of TMAs for GOG-0213 to study markers of recurrence, survival and treatment response or resistance. The specific types of the TMAs that can be created will depend on the paraffin block submissions for this protocol and the clinical outcomes observed for these cases. For example, one TMA could contain matched cores of tumor collected prior to initiating first-line and second-line therapy with adjacent normal tissue from secondary cytoreductive surgery whereas another TMA could represent tumor cores from patients who experienced short survival, intermediate survival or long survival or include tumor cores from patients treated on a specific treatment arm who experienced short, intermediate or long progression-free survival.

### 7.33 Laboratory Testing**(06/22/09)**

Staff at the GOG Tissue Bank will coordinate with the Chairs of the GOG Committee for Experimental Medicine and the Tissue Utilization Subcommittee as well as staff in the GOG Statistical and Data Center to distribute appropriate specimens to approved investigators for testing for this trial. Investigators will be responsible for completing the approved testing and transferring appropriate laboratory data with accurate specimen identifiers to the GOG Statistical and Data Center for analysis. The study chair for GOG-0213 will coordinate study co-chairs, scientific collaborators and members of the GOG Statistical and Data Center as needed to perform appropriate statistical analysis and to prepare abstracts, presentations, reports and manuscripts.

Appropriate unstained sections from conventional blocks and/or TMAs, aliquots of serum or plasma, and specified concentrations of DNA with

appropriate Q/C data will be distributed to Dr. Michael Birrer at MGH Cancer Center and/or to investigators approved by the GOG Committee on Experimental Medicine for biomarker, genomic, proteomic and SNP analyses based on available funding and expertise. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the GOG-0213 tissue specimens, serum, plasma and DNA from whole blood will be reevaluated based on evolving data in the field. All bioinformatics and statistics will be performed as a collaboration with the GOG Statistical and Data Center.

7.331 Light Microscopy

Light microscopy will be performed using formalin-fixed and paraffin-embedded tissue specimens to characterize the histopathologic features of the tissue specimens undergoing molecular and biochemical profiling, and to satisfy some of the specimen election criteria for gene expression profiling. Stained specimens will be reviewed by Dr William Rodgers (chair of the GOG Pathology Committee) and other members of the Pathology Committee.

7.332 Biomarker Analysis**(06/22/09)**

Multiple types of biomarker analyses will be performed to expand our current understanding of the biology, progression, metastasis and responsiveness of recurrent ovarian and peritoneal primary cancer. Immunohistochemistry assays will be performed as needed in sections from conventional paraffin blocks and the GOG-0213 TMAs in Dr Michael Birrer's laboratory at the MGH Cancer Center, the GOG Receptor Core Laboratory, and/or by investigators approved by the

Committee on Experimental Medicine based on available funding and expertise. Reverse phase array and conventional immunoblot analyses will be performed as needed in lysates from frozen recurrent tumor tissue, microdissected recurrent tumor cells and normal tissue. Quantitative RT-PCR will be performed as needed using specific primers in RNA extracted from the appropriate type of tissue specimens. These assays will be used to identify and/or validate prognostic or predictive markers of recurrent, survival and treatment response or resistance. In addition, these assays will be used to validate individual markers identified in gene expression microarray studies (see below).

7.333 Genomic Profiling**(06/22/09)**

Gene expression microarray analysis will be undertaken using RNA isolated from frozen recurrent tumor and normal tissue to define gene expression patterns associated with disease progression, spread of disease, response to treatment or patient outcome. These studies will utilize an Affymetrix platform or an appropriate alternative and will be performed in Dr Michael Birrer's laboratory at the MGH Cancer Center and by investigators approved by the Committee on Experimental Medicine based on available funding and expertise.

7.334 Proteomic Profiling**(08/04/08) (06/22/09)**

Proteomic profiling will be performed in pre-op serum specimens to define protein/peptide fragment patterns that are associated with disease progression, spread of disease, and response to treatment or patient outcome. All proteomic studies will be performed by a Proteomic Group approved by the GOG Committee on Experimental Medicine based on available funding and expertise.

7.335 SNP Analysis**(06/22/09)**

The 10 ml of whole blood (WB01) drawn into a standard purple-top Vacutainer® tube with EDTAwill be shipped to the GOG Tissue Bank in Columbus, OH for immediate processing, extraction of DNA and Q/C assessments. Staff at the GOG Tissue Bank will be responsible for shipping an appropriate quantity of DNA with corresponding Q/C data to Dr. Michael Birrer at MGH Cancer Center and/or investigators approved by the Committee on Experimental Medicine based on available funding and expertise for whole genome SNP-associations studies and/or evaluation of individual SNPs.

7.34 Future Research**(06/22/09)**

See Section XII in Appendix III for important details regarding the banking and distribution of the residual tumor specimens, normal tissue, serum, plasma and normal DNA from blood still remaining after completion of GOG-0213 for future research.

7.4 Quality of Life: **(08/04/08)**

7.41 Patients in the secondary cytoreduction arm will complete the quality of life questionnaire packet (which includes the FACT-O and the RAND SF-36 physical functioning questionnaire) before surgery and before the first

cycle of chemotherapy. The FACT-O is available in Spanish and French. Requests should be submitted to the GOG Statistical and Data Center. Patients in the no surgery arm will complete the quality of life questionnaire packet before the first cycle of chemotherapy. Follow-up questionnaires will be completed prior to beginning of the third cycle (approximately six weeks from the start of treatment) and prior to beginning of the sixth cycle (or approximately 15 weeks from the start of treatment). Additional quality of life assessments will be done at six and twelve months after initiating chemotherapy. If a patient progresses or is removed from the study treatment, continue to follow the schedule of QOL assessments when possible regardless of subsequent treatments. Whenever possible, QOL questionnaires should be administered at the clinic visit before the patient is seen by the physician and before evaluations (e.g., results of CA-125 or scans) are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.42 The Quality of Life Liaison (Nurse\Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.43 The Nurse\Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.

7.44 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.45 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing patient's response.

7.46 Review the questionnaire for completeness before the patient leaves.

7.47 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.48 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.49 It is essential that questionnaires be completed according to the schedule described in Section 7.1.

7.410 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

7.411 The patient may withdraw from the quality of life section of the protocol for any reason. The reason must be documented on the form.

7.412 The Quality of Life Liaison may attend a training session held at a biannual GOG meeting.

# 8.0 EVALUATION CRITERIA

## 8.1 Parameters of Response – GOG RECIST Criteria

### 8.11 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

### 8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

### 8.13 Best Response

Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline. *Reporting of these changes in an individual case should be in terms of the* ***best response*** *achieved by that case since entering the study*.

8.131 Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart. Normalization of CA125, if elevated at baseline, is required for ovarian carcinoma studies.

8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.

8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 8 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.

8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

8.135 Stable Disease is any condition not meeting the above criteria.

8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.

8.14 Progression (measurable disease studies) is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression

- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided) **(06/22/09)**
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

      - or -
    - Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

      - or -
    - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

      When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression.**(08/23/10)**

Progression (non-measurable disease) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

      - or -
    - Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

- or -

- Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression.**(08/23/10)**

8.15 Recurrence (following CR) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Increase in serum CA-125 levels as follows:
  - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

8.16 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.

8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.

8.19 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v3.0.

## 9.0 DURATION OF STUDY

9.1 Patients will remain on the designated study regimen until disease progression or toxicity precludes further treatment or the patient refuses study treatment.

9.2 All patients will be followed (with completion of all required case report forms) until disease progression, or the patient withdraws consent. In addition, following disease progression, patients will be monitored for delayed toxicity and survival for a period of 10 years with Q forms submitted to the GOG Statistical and Data Center, unless patient's consent is withdrawn.

# 10.0 STUDY MONITORING AND REPORTING PROCEDURES

## 10.1 ADVERSE EVENT REPORTING FOR A TRIAL EVALUATING A SURGICAL PROCEDURE **(09/29/14)**

### 10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease that occurs in a patient administered a pharmaceutical product or protocol procedure, whether the event is considered related or unrelated to the study treatment.

### 10.12 Reporting Expedited Adverse Events

All CTCAE v3.0 expedited AEs must be reported to the GOG. All expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (CTEP-AERS). Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting.

### 10.13 Expedited Reporting of Adverse Events occurring within 30 Days of the Study Procedure

The following table summarizes the GOG requirements for expedited reporting of AEs that occur **within** 30 days of the surgical procedure.

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Study Procedure:

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the CTEP-AERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitali-zation | Without Hospitali-zation | With Hospitali-zation | Without Hospitali-zation | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 7 Days | Not Required | 7 Days | Not Required | 7 Days | 7 Days |
| **Possible Probable Definite** | Not Required | Not Required | Not Required | 7 Days | Not Required | 7 Days | Not Required | 7 Days | 7 Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting as follows:

CTEP-AERS 7 calendar day report:
- At least Grade 3 with hospitalization or prolongation of hospitalization, or
- Persistent causes, significant disabilities/incapacities

[2] **Grade 5:** All deaths within 30 days of the surgical procedure must be reported within 7 calendar days using expedited reporting regardless of causality.

**Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to Expedited Reporting Requirements for Surgical Trials."**

**March 2005**

- Expedited AE reporting timelines defined:
  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grades 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities and/or incapacities must be reported via CTEP-AERS if the event occurs following a protocol procedure.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Surgical Trials:

- There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. **(09/26/11)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.2 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT (TO USE FOR PATIENTS WHO SELECT BEVACIZUMAB AFTER AUGUST 28, 2011) **(12/19/11)**

10.21 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

10.22 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS serves as notification to GOG,

and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.23 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the CTEP-AERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days |
| **Possible Probable Definite** | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days | 7 Calendar Days | Not Required | 24-Hrs; 3 Calendar Days | 7 Calendar Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under section entitled "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND."**

March 2005

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) with the exception as listed below (grade 2-4 myelosuppression) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- Reference the SPEER (Specific Protocol Exceptions to Expedited Report) for the subset of AEs that are protocol specific exceptions to expedited reporting via CTEP-AERS. Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If the CAEPR for a protocol agent is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required. For questions or comments

regarding the SPEER or CAEPR, please contact the CTEP-AERS MD Help Desk at CTEP-AERSmd@tech-res.com**(12/19/11)**

- *"All Grades 2, 3 and 4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) regardless of the need for hospitalization is exempt from expedited reporting*."

10.24 Procedures for Expedited Adverse Event Reporting:**(12/19/11)**

10.241 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The NCI guidelines for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.**(09/26/11)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.25 Automated CDUS reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through CTEP-AERS will also be included with the quarterly CDUS data submissions.

10.3 ADVERSE EVENT REPORTING FOR A COMMERICIAL AGENT (TO BE USED FOR PATIENTS NOT TAKING BEVACIZUMAB AFTER AUGUST 28, 2011) **(08/29/11) (12/19/11)**

10.31 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the CTEP-AERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitalization | Without Hospitalization | With Hospitalization | Without Hospitalization | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days |
| **Possible Probable Definite** | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days | 7 Calendar Days | Not Required | 24-Hrs; 3 Calendar Days | 7 Calendar Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005**

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

**The following events should be excluded from CTEP-AERS reporting, although they should still be reported to the routine AE CRFs:**

- Grade 3 or 4 myelosuppression, with or without hospitalization **(12/19/11)**

- There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.32 Procedures for Expedited Adverse Event Reporting:

10.321 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-possibly related to cancer treatment (specify)".

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.33 Automated CDUS reporting

For studies using commercial agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through CTEP-AERS will also be included with the quarterly CDUS data submissions.

10.4 GOG DATA MANAGEMENT FORMS (08/04/08) (06/22/09) (03/15/10)

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except: F-form, Pathology report, OP report and QOL forms should be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). Quality of Life questionnaires are to be completed on Scantron forms and submitted by mail. Pathology material (F-form, path report and slides) should be submitted together via mail.

| Form± | Due within | | Copies * | Comments |
|---|---|---|---|---|
| | Weeks | Event | | |
| Form R (Registration Form) | 2 | Registration | 1 | Mandatory Submission via SEDES |
| Form OSR (Recurrent Gynecologic Cancer - On Study Form) | 2 | Registration | 1 | Mandatory Submission via SEDES |
| Specimen Consent Application | 1 | Registration ° | N/A | Complete Online |
| Form DR (Pretreatment Summary Form | 2 | Registration | | Mandatory Submission via SEDES |
| Form D2M (Solid Tumor Evaluation Form) # | 2 | Registration | 1 | Mandatory Submission via SEDES |
| Primary Disease | | | | |
| Form F (Pathology Form) | 6 | Registration | 3 | Submit together to the |
| Pathology Report | 6 | Registration | 3 | SDC via postal mail |
| Pathology Slides | 6 | Registration | ** | |
| Secondary Cytoreductive Surgery | | | | |
| Form F (Pathology Form | 6 | Surgery*** | 3 | Submit together to the |

| | | | | |
|---|---|---|---|---|
| Pathology Report | 6 | Surgery*** | 3 | SDC via postal mail |
| Cytoreductive Surgery:<br>Form C (Surgical Reporting Form)<br>Operative Report<br>Discharge Summary | <br>6<br>6<br>6 | Surgery*** | <br>1<br>2<br>2 | Mandatory Submission via SEDES<br><br>Submit via postal mail<br>Submit via postal mail |
| Form SP-FT01-0213 for archival formalin-fixed and paraffin-embedded (FFPE) primary or metastatic tumor (FT01):<br>1st choice: Block<br>2nd choice: 16 Unstained Slides | 8 | Registration | | Submit via SEDES *ƒ*<br>Ship block or unstained slides for translational research with a copy of the SP Form for FT01 to the GOG Tissue Bank in Columbus Ohio†∇ |
| Form SP-SB01-0213 for frozen pre-op serum in ten cryotubes | 1 | Surgery*** | | Submit via SEDES *ƒ*<br>Ship with a copy of appropriate SP Forms to the GOG Tissue Bank in Columbus Ohio‡∇ |
| Form SP-PB01-0213 for frozen pre-op plasma in ten cryotubes | 1 | Surgery*** | | |
| Form SP-FR01-0213 for fixed recurrent tumor in formalin jar or paraffin block | 1 | Surgery*** | | |
| Form SP-RR01-0213 for frozen recurrent tumor | 1 | Surgery*** | | |
| Form SP-FN01-0213 for fixed normal tissue in formalin jar or paraffin block | 1 | Surgery*** | | |
| Form SP-RN01-0213 for frozen normal tissue | 1 | Surgery*** | | |
| Form SP-WB01-0213 for whole blood (WB01) to be shipped at ambient temperature the day the blood is collected ‡‡ | 26 | Registration<br>(except where noted in the patient form schedule) | | Submit via SEDES.*ƒ*<br>Ship the whole blood with a copy of the SP Form for WB01 to the GOG Tissue Bank in Columbus Ohio‡‡ |
| Form T (Common Toxicity Reporting Form) -post op**** # | 2 | Surgery*** | 1 | Mandatory Submission via SEDES |
| Form D2R-Cycle Dose Drug Form #<br> | 2<br>2 | Completion of each cycle of therapy | 1 | Mandatory Submission via SEDES |
| Form T (Common Toxicity Reporting Form) # | 2 | Beginning of each subsequent cycle | 1 | Mandatory Submission via SEDES |
| Form D2M (Solid Tumor Evaluation Form) # | 2 | Clinical response assessment | 1 | Mandatory Submission via SEDES |
| Form BMR (Biomarker Reporting Form) ± | 2 | Prior to surgery, prior to each cycle of therapy and during follow-up | 1 | Mandatory Submission via SEDES |
| FACT-O**** (Scantron Form) | 2 | Prior to surgery | 1 | If randomized to surgery submit the original |

| | | | | |
|---|---|---|---|---|
| | | | | Scantron form to the GOG SDC via postal mail |
| FACT-O**** (Scantron Form) | 2 | Prior to cycle 1, 3 and 6 and at 6 and 12 months after starting chemotherapy. | 1 | Submit the original Scantron form to the GOG SDC via postal mail |
| Form SRGSTAT (Surgical Status Form) | 52 | Registration | 1 | Mandatory Submission via SEDES |
| Form Q0 (Treatment Completion Form | 2 | Completion of study treatment | 1 | Mandatory Submission via SEDES |
| Form Q (Follow-up Form) | 2 | Disease progression, death, and post-treatment follow-up | 1 | Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years, yearly thereafter |

* The number of required copies including the original form which must be sent to the Statistical and Data Center if the forms are not submitted via SEDES. No copies are required for forms submitted through SEDES. Forms submitted through SEDES should not be sent through postal mail or fax.

** Pathology slides are required for central review by the GOG Pathology Committee. See Section 7.4 for details.

*** Patients who are randomized to surgical cytoreduction, submit after surgery.

**** Submit original Scantron QOL forms and coversheet to the GOG Statistical and Data Center. The patients randomized to cytoreductive surgery undergo an assessment prior to surgery as well as prior to initiating chemotherapy.

± Serial CA-125 values should be reported on Form BMR

# In the event that it becomes necessary to modify the dose or stop individual study agents for either protocol directed reasons or other reasons, continue to submit D2R, T and D2M forms until all study agents are stopped or another anti-cancer therapy is initiated.

º Required only for patients randomized to undergo secondary cytoreduction surgery.

▽ Required for patients randomized to undergo secondary cytoreductive surgery Appendix III**(08/04/08)**

*f* Form SP **must be submitted online** to the GOG SDC using SEDES regardless of whether the specimen is submitted for research.

† See footnote 3 in the Quick Scan Summary in Section 7.31 of the protocol and Section IX of Appendix III for important details for shipping FT01 to the GOG Tissue Bank with a completed SP Form, and for instructions for how to have an optional SP Form for FT02 loaded to the patient form schedule.

‡ See footnote 6 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix III for important details for shipping the surgical specimens including FR01 and RR01 and any of the optional high priority specimens (FN01, RN01, SB01 and PB01) to the GOG Tissue Bank with the corresponding SP Forms.

‡‡ See footnote 7 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix III for important details for shipping WB01 to the GOG Tissue Bank with the corresponding SP Form.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested.**(09/26/11)**

## 11.0 STATISTICAL CONSIDERATIONS

### 11.1 Randomization**(10/01/12)**

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies: (All patients enrolled after August 28, 2011 will have their surgical cytoreductive treatment determined through randomization. These patients will select one of the following systemic treatments and declare their selection prior to enrollment onto the study) **(08/29/11)(12/19/11)**

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 GC: A standard regimen consisting of carboplatin (AUC 4) day 1 and gemcitabine (1000 mg/$m^2$) day 1 and 8 for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.13**CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment.

11.14 GCB: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until toxicity or progression necessitates discontinuing treatment early.

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.15 No cytoreductive surgery

11.16 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments (this sentence applies only to patients enrolled prior to Aug 29, 2011, thereafter patients select either CT, GC, GCB or CTB as their systemic treatment.). For those who consent to have cytoreductive surgery determined through randomization,

the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study.**(08/29/11)**

11.2 Measures of Efficacy and safety

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

11.3 Treatment efficacy

*Overall type I error:* This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

*Expected median survival on the standard treatment:* Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

*Accrual target for evaluating the efficacy of systemic therapy*
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

*Statistical power for evaluating the efficacy of biologic therapy*: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: $H_{01}$: $\Delta_{01} = \lambda_{CTB} / \lambda_{CT} \geq 1$will be assessed, where $\lambda$.is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their randomly assigned treatment. This comparison will not include those patients who were enrolled after August 28, 2011 and hence selected their systemic treatment. The

type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months).**(08/29/11)(12/19/11)**

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

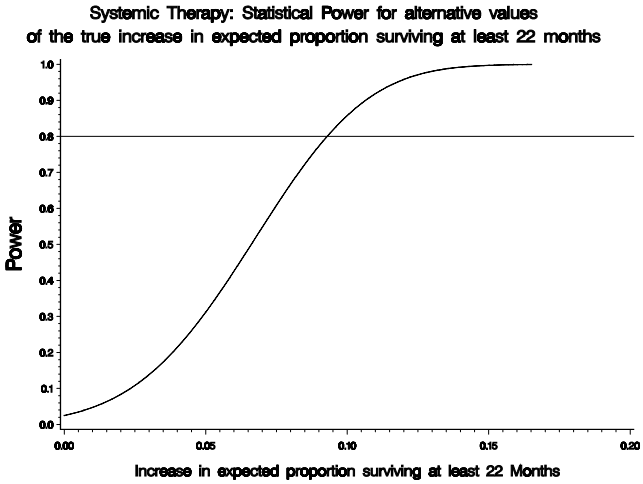



**Figure 1.**

*Statistical Power- evaluating the efficacy of surgical cytoreduction*: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival ($H_{02}$: $\Delta_{02} = \lambda_{surgery} / \lambda_{No\ surgery} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their randomly assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment (CT vs CTB vs. CG vs CGB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12

months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses. **(08/29/11)(10/01/12)**

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, $H_{02}$, when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2. The anticipated total accrual for this component of the study is 360 patients.**(08/29/11)**

*An addendum to the statistical considerations following the amendment to extend recruitment to the surgical component of the study.* ***(12/19/2011)***

As of Nov-1-2011, there were 114 patients enrolled onto the surgical component of this study and 17 of these patients had died. The planned total number of patients to be enrolled onto the surgical component of this study is 360 patients. There were 35 patient enrolled during 2010, and 34 patients are projected to be enrolled during 2011. Therefore, assuming the future accrual is 35 patients per year, this study is expected to complete its targeted accrual in 7 years (Nov-2018). Patients enrolled after Aug-28-2011 will have their cytoreductive surgery determined by randomization. All of these patients will receive a standard carboplatin-paclitaxel regimen and permitted to choose whether to have bevacizumab supplement their treatment.

The data currently available from GOG-0213, indicates that the marginal hazard of death is approximately 0.021 $month^{-1}$. Assuming a constant hazard, the expected number of deaths when the accrual is completed among the 114 patients, who are already enrolled onto the surgical component of this study is 97.4. Assuming a similar death rate for all future patients, Simpson's rule (Schoenfeld, Biometrics 1983) can be used to estimate the number of patients among those who will be enrolled over the next 7 years and will have died when the accrual has been completed (130.1 deaths). Hence the expected total number deaths at the time when the target accrual is completed is 97.4+130.1 = 227.5. Likewise, the expected number of deaths reported 9 months after the targeted accrual is complete is 100.2+150.0=250.2, which is approximately the number required for the final analysis.

Therefore, the targeted date for completing the accrual to the surgical component of this study is Fall-2018. The required number of deaths required for the final analysis (250 deaths) is expected to occur nearly 1 year after the targeted accrual has been completed. In the event that the required number of deaths for the final analysis is observed before the targeted accrual is completed, then accrual will be stopped prior to attaining the targeted accrual. The planned analyses and the

power calculations provided above are unchanged by this revised recruitment plan.**(12/19/2011)**

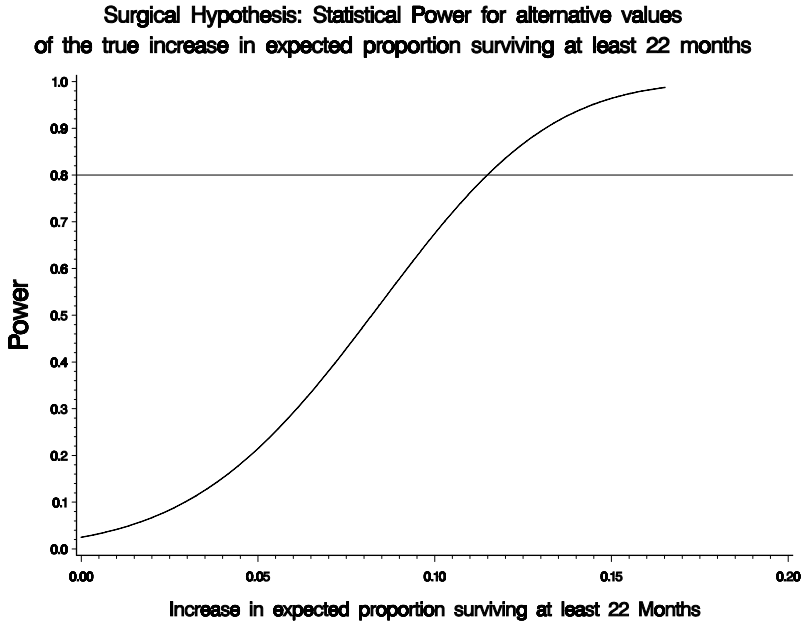



**Figure 2.**

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin with or without bevacizumab. It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.**(08/29/11)**

*Interim Analyses:* Interim analyses are planned when there are at least 110 deaths reported among all those patients randomly allocated (prior to August 29, 2011) to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and

July each year and the precise date of these meetings is set without confidential knowledge of the study results. **(10/01/12)**

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those randomly allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information time, $H_{01}$ will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis. **(08/29/11)**

$H_{02}$ will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of $H_{02}$ will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for $H_{01}$ (or $H_{02}$) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $\Delta_{01} > 1.0$ (or $\Delta_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%. The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

*Final analysis:* The study will be considered sufficiently mature to permit a final assessment of $H_{01}$ when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of $H_{02}$ when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the

O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

*Supplemental final analyses:* A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

*Safety Analyses:* The GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities, serious adverse event (SAE) reports and deaths in which study treatment may have been a contributing cause. This committee does not review efficacy results. The DSMB may recommend study amendments pertaining to patient safety.

Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

## 11.4 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

*Construct and content*
The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items) [43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

*Descriptive analyses of baseline QOL scores*
Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean, standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

*Differences in FACT-TOI scores between patients receiving CT and CTB:* Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation

between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

*Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

*Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery.* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

## 11.5 Translational Research Statistical Considerations

*Overview*
The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

*Anticipated sample size for translational objectives*
The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately 198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1.

Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

*Training and validation set*
In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.

*Identifying biologic/molecular profiles*
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

*Reliability*
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which cannot be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

*Validation*
Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-

index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is known to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators, since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.6 The anticipated distribution of patients' race and ethnicity for the systemic therapy
portion of this trial is (all are female):

| | |
|---|---|
| White (not Hispanic) | 584 |
| Black (not Hispanic) | 39 |
| Hispanic | 14 |
| Asian | 17 |
| American Indian or Alaskan Native | 3 |
| Native Hawaiian or other Pacific Islander | 3 |

## 12.0 BIBLIOGRAPHY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# APPENDIX I

## FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

(1985)

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

| | |
|---|---|
| Stage I | Growth limited to the ovaries. |
| Stage IA | Growth limited to one ovary; no ascites.<br>No tumor on the external surface; capsule intact. |
| Stage IB | Growth limited to both ovaries; no ascites.<br>No tumor on the external surfaces; capsules intact. |
| Stage IC* | Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings. |
| Stage II | Growth involving one or both ovaries with pelvic extension. |
| Stage IIA | Extension and/or metastases to the uterus and/or tubes. |
| Stage IIB | Extension to other pelvic tissues. |
| Stage IIC* | Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings. |
| Stage III | Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor is limited to the true pelvis but with histologically verified malignant extensions to small bowel or omentum. |
| Stage IIIA | Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces. |
| Stage IIIB | Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative. |
| Stage IIIC | Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes. |
| Stage IV | Growth involving one or both ovaries with distant metastasis. If pleural effusion is present there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV. |

* In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

APPENDIX II

SECONDARY CYTOREDUCTIVE SURGICAL PROCEDURE

Purpose : Maximum resection of recurrent ovarian cancer.

Timing: Surgical exploration should be undertaken within 4 weeks of study entry.

Content of Procedure:

1.0 The abdominal incision must be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. A vertical incision is recommended but not required.
2.0 All peritoneal surfaces including the undersurface of both diaphragms and the serosa and mesentery of the entire gastrointestinal tract will be visualized and palpated for evidence of metastatic disease.
3.0 Visible metastatic abdominal and pelvic disease should be resected or ablated completely, if possible.
4.0 Diaphragmatic recurrent disease should be resected. Ablation of disease with electrocautery (e.g. Argon Beam Coagulator) is acceptable.
5.0 Surgical evaluation of the pelvic and paraortic node bearing areas requires resection if not performed on initial staging/debulking procedure. If incomplete nodal resection was previously documented, unresected areas should be excised.
6.0 Solid organ metastases (spleen and liver) should be considered for resection. Treatment by Radio Frequency Ablation (RFA) is acceptable.

Goal: Surgical goal of cytoreduction is to reduce volume of residual disease to smallest quantity possible (no visible residual).

Reporting: The size (two dimensions) and location of residual disease will be recorded.

APPENDIX III

# I. Quick Scan Summary of the Specimen Requirements for GOG-0213.

Refer to Section 7.31 of the Protocol for a copy of the Quick Scan Summary Table.

# II. Obtaining a GOG Bank ID for Any GOG Protocol (1/3/11)

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient, and all specimens and accompanying paperwork for each patient must be labeled with this coded and confidential tracking number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website under Tools on the Web Menu page.

Obtain the GOG patient study ID for any GOG protocol with specimen requirements other than GOG-0136 (specimen banking protocol) before requesting a GOG Bank ID from the Tissue Bank Portal.

Please contact the User Support Department at the GOG Statistical and Data Center at support@gogstats.org or by phoning 716-845-7767 or the staff in the GOG Tissue Bank by phoning 866-464-2262 or faxing 614-722-2897 if you need assistance.

# III. Requesting Specimen Kits for GOG-0213

## A. Ordering Specimen Kits for GOG-0213

1. A Dual-Chamber Specimen Kit can be ordered for each GOG-0213 patients who are randomized to the surgery arm of this study from the GOG Tissue Bank using the GOG Tissue Bank's Kit Management application. This application can be accessed via the GOG Web Menu. Plan ahead so that the kits can be shipped by ground transportation whenever possible. **This kit must only be used for the submission of the GOG-0213 pre-op serum and pre-op plasma specimens and the recurrent tumor and normal tissue collected during secondary cytoreductive surgery.** Please submit the archival formalin-fixed and paraffin-embedded primary or metastatic tumor specimen (block or 16 unstained sections) in your own container**.** For shipping information, please see Section IX.
2. Replacement kits can be ordered as needed based on the number of patients enrolled by your institutions on this protocol and randomized to have secondary cytoreductive surgery. Always try to have replacements available.

## B. Materials Provided in the Specimen Kit for GOG-0213

Each Specimen Kit for GOG-0213 will consist of a dual-chamber shipping container for shipping the frozen pre-op serum (SB01), frozen pre-op plasma (PB01), frozen recurrent tumor (RR01) and frozen normal tissue (RN01) on one side and the formalin-fixed recurrent tumor (FR01) and formalin-fixed normal tissue (FN01) on the other side. The following supplies will also be provided within each GOG-0213 kit: foil to wrap the two frozen tissue specimens if snap frozen, two truncated OCT embedding molds if the two types of tissue are OCT-embedded and frozen, two 15-ml screw-cap polypropylene conical tube, two plastic disposable transfer pipette for mixing the serum and plasma specimens, two sets of five 1.8 ml screw-cap cryogenic vials (cryotubes) for the serum aliquots, two sets of five 1.8 ml screw-cap cryogenic vials (cryotubes) for the plasma aliquots, two 15 ml formalin jars for two types of fixed tissue, four plastic zip-lock bags for the frozen specimens, two secondary shipping envelopes with absorbent material, a dry ice label (UN1845), an Exempt Human Specimen Sticker and a pouch for the shipping label.

If there are supplies required to satisfy the specimen requirements for this protocol that are not in provided in the GOG-0213 Specimen Kit or are not available in your clinic, department or institution, please contact the staff at the GOG Tissue Bank by phoning 866-464-2262 (866-GOG-BANC) who will try to help you obtain these additional supplies when possible.

### C. Unused Materials or Unused Specimen Kits for GOG-0213

Unused materials or unused Specimen Kits for GOG-0213 will need to be returned to the GOG Tissue Bank. Contact the GOG Tissue Bank if you have any question about the return of unused material.

## IV. Submitting Archival Primary or Metastatic Tumor for GOG-0213

### A. Requirement

**Archival formalin-fixed and paraffin embedded (FFPE) primary or metastatic tumor tissue (FT01)** will only be required from women on GOG-0213 who undergo secondary cytoreductive surgery and give permission for their tissue (tumor and/or normal tissue) to be submitted and used for this research study. Patients may participate in this treatment protocol even if they don't give permission for their tissue to be submitted and used for this research study. If tumor cannot be submitted for GOG-0213, please indicate the reason in item 5 on the SP Form such as patient refused, not enough tumor for research, or referring site won't release tumor.

### B. Purpose

The GOG Tissue Bank will collaborate with the GOG Statistical and Data Center and the GOG Tissue Utilization Subcommittee to design and create a series of tissue microarrays (TMAs) for GOG-0213 to study markers of recurrence, survival and treatment response or resistance, and prepare sections from conventional blocks and TMAs as needed. Unstained sections from conventional blocks and TMAs will then be distributed to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker, proteomic and genomic analyses. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in this specimen will be reevaluated based on evolving data in the field.

### C. Time Point

The archival formalin-fixed and paraffin-embedded primary or metastatic tumor tissue must have been collected prior to initiating primary chemotherapy. There may be certain patients who receive neoadjuvant chemotherapy prior to surgery, and these details will need to be declared in item 15 of the SP Form for this specimen including agent names with treatment start and stop dates.

### D. Format for Labeling the Specimen

Label the archival primary or metastatic tumor specimen (formalin-fixed and paraffin-embedded) with the GOG protocol number (GOG-0213), GOG Bank ID (####-##-G###), specimen code (FT01 for archival formalin-fixed tumor tissue), and collection date (mm/dd/yyyy). This specimen may also be labeled with the pathology accession number and block identifier, but must not be labeled with personal identifiers like patient name or initials.

### E. Instructions for Submitting the Archival Primary or Metastatic Tumor Tissue

1. **Identify an Appropriate Tumor Specimen.** Every attempt should be made to provide a tumor block for this research study. Primary tumor is the first choice and metastatic tumor is the second choice. If both can be submitted the primary tumor should be labeled FT01 and the metastatic tumor should be labeled FT02. If it is not possible to provide a block on a permanent or temporary basis, the back-up option will be to provide sixteen unstained sections, 5 micrometer in thickness, on charge glass slides suitable for a standard immunohistochemistry assay. If your institution can not permanently provide a tumor block for this research study, please urge the Pathology Department to allow a tumor block to be submitted to the GOG Tissue Bank on a temporary basis. In this case, please state in field 15 on the SP

Form for FT01 that the tumor block must be returned after the unstained sections and cores for TMA creation are obtained.

2. **Label Tumor Specimen.** Label the primary or metastatic tumor specimen (block or unstained sections) with the GOG protocol number, the GOG Bank ID, the Specimen Code and the collection date.
   * ***Use FT01 for the formalin-fixed primary or metastatic tumor tissue. If both are submitted, use FT01 for the primary tumor and FT02 for the metastatic tumor. The SP Form for FT02 would be considered an optional form for this protocol. In this event, please contact the GOG Statistical and Data Center to have the additional SP Form for FT02 added to the patient form schedule.***
3. **Complete the Form SP**. Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, submit a copy to the GOG Statistical and Data Center online or by fax, and retain a copy in your files.
   * ***The type of tumor tissue (primary or metastatic) and specimen (block or sections) will need to be specified on the specimen transmittal form (Form SP) submitted for FT01 for GOG-0213. If sections are submitted instead of a tumor block, the reason must be stated in field 15 on the SP Form for this specimen (i.e., the Pathology Department at your institution is prohibited by local or state law from releasing blocks on a permanent or temporary basis for any reason). There may be certain patients who receive neoadjuvant chemotherapy prior to surgery, and these details will need to be declared in item 15 of the SP Form for this specimen including agent names with treatment start and stop dates.***
4. **Ship the Tissue Specimen(s).** Ship the archival tumor specimen(s) (block or unstained sections) to the GOG Tissue Bank **in your own shipping container** as described in Section IX. The archival tumor may also be included in the dual chamber kit if available when the other specimens are ready to ship to the Bank.

# V. Fixing and Freezing Recurrent Tumor and Normal Tissue for GOG-0213

## A. Requirement

The recurrent tumor will be excised during secondary cytoreductive surgery and a portion will need to be FFPE or fixed in formalin whereas the remainder will need to be frozen (either snap-frozen or OCT-embedded and frozen). Normal tissue is an optional high priority specimen and if collected can either be FFPE or fixed in a jar with formalin whereas the remainder will need to be frozen (either snap-frozen or OCT-embedded and frozen).

**Fixed recurrent tumor (FR01)** will be required for all patients who give consent for some of their tumor tissue to be used for this research study and are randomized to have secondary cytoreductive surgery. A paraffin block of FFPE recurrent tumor (1st choice) or a piece of recurrent tumor in a jar with formalin (2nd choice) will need to be submitted to satisfy the FR01 requirement.

**Frozen recurrent (RR01)** will be required for all patients who give consent for some of their tumor tissue to be used for this research study and are randomized to have secondary cytoreductive surgery. A piece of recurrent tumor snap frozen and wrapped in foil or frozen in an OCT mold will need to be submitted to satisfy the RR01 requirement.

**Fixed normal tissue (FN01)** will be an **optional yet high priority requirement** for all patients who give consent for some of their normal tissue to be used for this research study and are randomized to have secondary cytoreductive surgery. A paraffin block of FFPE normal tissue (1st choice) or a piece of normal tissue in a jar with formalin (2nd choice) will need to be submitted to satisfy the FN01 requirement.

**Frozen normal tissue (RN01)** will be an **optional yet high priority requirement** for all patients who give consent for some of their normal tissue to be used for this research study and are randomized to have secondary cytoreductive surgery. A piece of normal tissue snap frozen and wrapped in foil or frozen in an OCT mold will need to be submitted to satisfy the RN01 requirement.

**B. Purpose**

The GOG Tissue Bank will create paraffin blocks from the formalin-fixed recurrent tumor and normal tissue, core appropriate paraffin blocks to create the GOG-0213 tissue microarrays (TMAs), and prepared sections from conventional blocks and TMAs as needed. Unstained sections from conventional blocks and TMAs will then be distributed to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker, proteomic and genomic analyses. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in these specimens will be reevaluated based on evolving data in the field.

**C. Time Point**

The fixed and frozen recurrent tumor tissue and normal tissue will be collected during secondary cytoreductive surgery.

**D. Format for Labeling the Specimen**

Label the tissue specimens from the secondary cytoreductive surgery procedure with the GOG protocol number (GOG-0213), the GOG Bank ID (####-##-G###), the specimen code (see below) and the collection date (mm/dd/yyyy).

- FR01 for the fixed recurrent tumor tissue
- RR01 for the frozen recurrent tumor tissue
- FN01 for the fixed normal tissue
- RN01 for the frozen normal tissue

**E. Recommendations for Preparing Fixed or Frozen Tissue Specimens**

*How quickly should tissue be fixed or frozen?* The tissue should be fixed or frozen as quickly as possible. Ideally within 30-60 minutes but certainly within 4 hours of excision from the patient. The faster these specimens can be fixed or frozen, the more valuable the specimens are for research. It may be appropriate to hold occasional meetings of surgical, laboratory, and clinical personnel to emphasize the urgency of processing these specimens rapidly.

*What type of freezing method should be used?* There are two types of freezing methods provided for your consideration: snap-freezing or OCT-embedding and freezing. When preparing the tissue specimens from the secondary cytoreductive surgical procedure, the choice of freezing method is not mandated for GOG-0213.

*How much frozen tissue should be submitted?* **Please submit as much frozen tissue as possible for research. Gram quantities with individual pieces ranging from 1 to 5 $cm^3$ are ideal.** Larger amounts of tissue will allow for replicate laboratory testing and permit validation testing to be performed.

*Any suggestions for how to coordinate these efforts?* It may be helpful to have meetings among the staff members at your institution such as the GOG surgeons, GOG pathologists, general pathologist, operating room team, nurses, clinical research coordinators and/or tissue procurement specialist that will participate in procuring the tissue specimens for this component of GOG-0213 and a protocol like GOG-0136. These types of meetings can help clarify responsibilities and communication methods for keeping the appropriate individuals appraised as to when their services will be need to satisfy the tissue requirements for this protocol. Sharing operating schedules and providing updates on how the surgery is progressing may help ensure that the members of the team are available when needed thus improving the working relationship among the team and the quality of the tissue specimens submitted for this protocol**.**

**F. Procedures For Excising Tissue For Research**

1. Excising recurrent tumor tissue during secondary cytoreductive surgery.
   a. The surgeon should send the excised recurrent tumor tissue from each GOG-0213 patient randomized to undergo surgery to the surgical pathology suite and arrange for immediate tissue sampling within 30-60 minutes of excision when possible.
   b. **Submit as much tumor tissue for research as possible. Gram quantities with individual pieces ranging from 1 to 5 $cm^3$ are ideal. There is a minimum requirement of 500 mg or 0.5 $cm^3$ (slightly larger than a pencil eraser).**
   c. The tumor tissue for submission to the GOG Tissue Bank will undergoing various types of laboratory testing and should be as clean and as free from necrosis as possible.
   d. Promptly following the dissection of the tumor sample, a piece of the recurrent tumor tissue must be formalin-fixed (FR01), and another piece must be snap-frozen or OCT-embedded and frozen (RR01) as described below.
2. Excising normal tissue during surgery.
   **a.** The surgeon should also try to excise a piece of normal tissue from each GOG-0213 patient randomized to undergo surgery and send it with the tumor tissue when it is sent to the surgical pathology suite so that tissue sampling can be performed within 30-60 minutes of excision when possible. **Normal tissue can be any normal epithelial tissue including non-involved ovary, fallopian tube, uterus, cervix, or skin. When normal epithelium is not available, please submit non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.** Please try to submit normal epithelium whenever possible as this type of tissue will serve as the most appropriate control for the laboratory testing to be preformed for this protocol. **Note for the pathologist,** in the unlikely event that any tumor tissue is subsequently identified within the normal tissue submitted for research, the Pathology Department at the treating institution will be informed and the material will be immediately returned for diagnostic purposes.
   b. Please submit **gram quantities with individual pieces ranging from 1 to 5 $cm^3$ when possible and a minimum of 500 mg or 0.5 $cm^3$ of normal tissue (slightly larger than a pencil eraser).**
   d. Promptly following the dissection of the normal tissue specimen, a piece of the normal tissue must be formalin-fixed (FN01) and another piece must be snap-frozen or OCT-embedded and frozen (RN01) as described below.

**G. Procedure For Formalin-Fixing A Tissue Specimen**

1. **Label the Formalin-Jar(s).** Label the formalin jar(s) provided in the specimen kit distributed by the GOG Tissue Bank for this protocol. Label each 15 ml formalin jar with the GOG protocol number, GOG Bank ID Number, appropriate Specimen Code, and collection date.
   * ***Use FR01 for the formalin-fixed recurrent tumor tissue and FN01 for the formalin-fixed normal tissue.***
2. **Transfer the Tissue into the Formalin-Jar.** Promptly following resection of the tissue, use forceps to transfer the tissue sample to the pre-labeled jar with 15 ml of 10% buffered formalin, securely fasten the lid, and wrap a piece of parafilm around the cap and lid several times.
3. **Store the Tissue in the Fixative.** Store tissue in the fixative in a 4ºC refrigerator until the fixed specimen is shipped to the GOG Tissue Bank (see below for shipping instructions). Please keep in mind that the formalin-fixed tissue specimen should undergo standard histologic processing and paraffin-embedding at the GOG Tissue Bank within 1-3 business days of collecting the tumor specimen when possible to avoid problems associated with excessive fixation that modify antigenicity and reduce the usefulness of the tissue specimen. **If the formalin-fixed tissue can't be shipped to the GOG Tissue Bank within 3 days of the surgery, please have your Pathology Department paraffin-embed this research specimen to preserve the usefulness of this specimen for research purposes. Pathologist review of this embedded tissue is not required, as this material has been designated for research. Alternatively, the formalin-fixed tissue can undergo standard histologic processing and be embedded in a paraffin block.**
4. **Complete Form SP.** Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Include a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.

- * ***Indicate if the tissue is recurrent tumor or normal tissue in field 22 on Form SP. If normal tissue, please specify the type of normal tissue that is being submitted in the comment field (item 15 on Form SP) such as normal ovary, Fallopian tube, uterus, cervix, skin, non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.***

5. **Ship the Tissue Specimen(s).** Ship the fixed tissue specimen(s) either in a jar(s) of formalin or embedded in a paraffin block to the GOG Tissue Bank as described in Section IX.

**H. Instructions for Preparing the Snap-Frozen Tissue**

1. **Label Zip-Lock Bag.** Using a waterproof marker, label a zip-lock bag supplied in the Dual-Chamber Specimen Kit distributed by the GOG Tissue Bank with the GOG protocol number, GOG Bank ID Number, the Specimen Code, and the collection date.
2. **Snap-Freeze Tissue**. Using forceps place the appropriate tissue specimen on a piece of foil supplied in the Single-Chamber Specimen Kit distributed by the GOG Tissue Bank, wrap the foil so that the specimen is completely covered and then immerse the tissue wrapped in foil in liquid nitrogen or a suitable substitute until the tissue is frozen solid.
3. **Transfer Snap-Frozen Tissue to Zip-Lock Bag**. Using forceps transfer the foil-wrapped frozen tissue specimen into the zip-lock baggie labeled with the GOG Bank ID Number, the appropriate Specimen Code and the collection date.
4. **Immediately Store Snap-Frozen Tissue**. Store the snap-frozen tumor in an appropriate ultra cold storage space such as an ultra cold freezer (≤ -70ºC), in liquid nitrogen (liquid or vapor phase) or in direct contact with excess dry ice until the specimens are shipped to the GOG Tissue Bank. A regular freezer (-20ºC) is not adequate. A cryostat is also not appropriate.
5. **Complete the SP Form**. Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, submit a copy to the GOG Statistical and Data Center online or by fax, and retain a copy in your files.
   - * ***Indicate that the item being shipped is a piece of snap frozen tumor in field 9 on Form SP. Alternatively, if a snap-frozen piece and an OCT-mold are both being submitted, select "Other" and enter "OCT-mold and piece" in the specify field. Also indicate if the tissue is recurrent tumor or normal tissue in field 22 on Form SP, and then specify the type of normal tissue that is being submitted in the comment field (item 15 on Form SP) such as normal ovary, Fallopian tube, uterus, cervix, skin, non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.***
6. **Ship the Tissue Specimen(s).** Ship the frozen tissue specimen(s) to the GOG Tissue Bank as described in Section IX.

**I. Instructions for Preparing the OCT-Embedding and Freezing Tissue**

1. **Label OCT-mold and Zip-Lock Bag.** Using a cryomarker, label a truncated OCT mold and Zip-Lock Bag supplied in the Single-Chamber Specimen Kit distributed by the GOG Tissue Bank with the GOG protocol number, GOG Bank ID Number, the Specimen Code, and the collection date. If more than 0.75 grams or 0.75 $cm^3$ of tissue is available for freezing, please split the tissue into two molds, each of which can be labeled with the same specimen code.
2. **OCT-Embed and Freeze the Tissue**. Cover the bottom of the mold with OCT embedding medium, and holding the mold with forceps place the mold in the vapor phase (not the liquid phase) of liquid nitrogen or a suitable substitute until the OCT becomes opaque and is no longer transparent. Do not allow the gel to become frozen solid. Using forceps place the appropriate tissue specimen into the thickened OCT pushing the specimen to the bottom of the mold. Add additional OCT to cover the tissue completely and to fill the mold approximately three-fourths full. Holding the mold with forceps, gradually immerse the entire mold into liquid nitrogen or a suitable substitute until the OCT and tissue are completely solid.
3. **Transfer Frozen OCT-Embedded Tissue to a Zip-Lock Bag**. Using forceps transfer the frozen OCT-embedded tissue specimen to the zip-lock bag labeled with the GOG Bank ID Number, the appropriate Specimen Code and the collection date.
4. **Immediately Store Frozen OCT-Embedded Tissue**. Store the frozen OCT-embedded tumor in an appropriate ultra cold storage space such as an ultra cold freezer (≤ -70ºC), in liquid nitrogen (liquid or

vapor phase) or in direct contact with excess dry ice until the specimens are shipped to the GOG Tissue Bank. A regular freezer (-20ºC) is not adequate. A cryostat is also not appropriate.

5. **Complete the SP Form**. Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, submit a copy to the GOG Statistical and Data Center online or by fax, and retain a copy in your files.
   * ***Indicate that the item being shipped is an OCT-mold in field 9 on Form SP. Alternatively, if an OCT-mold and a snap-frozen piece are both being submitted, select "Other" and enter "OCT-mold and piece" in the specify field. Also indicate if the tissue is recurrent tumor or normal tissue in field 22 on Form SP, and then specify the type of normal tissue that is being submitted in the comment field (item 15 on Form SP) such as normal ovary, fallopian tube, uterus, cervix, skin, non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.***
6. **Ship the Tissue Specimen(s).** Ship the frozen tissue specimen(s) to the GOG Tissue Bank as described in Section IX.

# VI. Preparing Frozen Serum and Plasma for GOG-0213

## A. Requirements and Purpose

A pre-op serum specimen and a pre-op plasma specimen will be an optional high-priority requirement for women who are randomized to undergo secondary cytoreductive surgery and consent to allow their serum and plasma to be prepared and used it for this research study.

- The pre-op serum specimen will need to be prepared after obtaining consent for this research study but prior to undergoing secondary cytoreductive surgery from 10 ml of blood drawn into a **plain red-top Vacutainer® tube** as described in Section VI-G, and shipped to the GOG Tissue Bank as described in Section IX.
- The pre-op plasma specimen will need to be prepared after obtaining consent for this research study but prior to undergoing secondary cytoreductive surgery from 10 ml of blood drawn into a **purple-top Vacutainer® tube** with the anti-coagulant EDTA as described in Section VI-H, and shipped to the GOG Tissue Bank as described in Section IX.

Patients may participate in this treatment protocol even if they don't give permission for some of their blood to be used for this research study. **If the serum or plasma specimens cannot be submitted for GOG-0213, please indicate the reason in item 5 on the SP Form, such as patient refused, tried but not able to draw blood, or Non-US site logistically infeasible.**

## B. Purpose

Serum and plasma will first be shipped to the GOG Tissue Bank in Columbus Ohio and then aliquots of the pre-op serum specimen and the pre-op plasma specimen will be distributed in batches to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker and proteomic analyses. The exact choice of the biomarkers and proteomic profiles to be evaluated and the assays to be performed in this specimen will be reevaluated based on evolving data in the field.

## C. Time Point

To pre-op serum specimen and the pre-op plasma specimen must be prepared after obtaining consent for this research study but prior to undergoing secondary cytoreductive surgery.

## D. Format for Labeling the Specimen

Label the serum specimens with the GOG protocol number (GOG-0213), the GOG Bank ID (####-##-G###), the specimen code (SB01 for the pre-op serum), and the collection date (mm/dd/yyyy).

Label the plasma specimens with the GOG protocol number (GOG-0213), the GOG Bank ID (####-##-G###), the specimen code (PB01 for the pre-op plasma), and the collection date (mm/dd/yyyy).

**E. Equipment and Supplies Needed for Preparing Serum Specimens**

In addition to the materials provided in each of the Specimen Kits for GOG-0213, you will need gloves, plain red-top Vacutainer® tube(s), tube rack, purple-top Vacutainer® tube with EDTA, a permanent marker, dry ice, a centrifuge, a refrigerator or a bucket with wet ice, and access to appropriate freezing/storage space to collect each serum specimen. ***If you do not have access to a plain red-top Vacutainer® tube and/or a purple-top Vacutainer® tube with EDTA, at your institution, please inform the staff at the GOG Tissue Bank who will try to provide you with these tubes when possible.***

**F. Guidelines and Recommendations for Preparing Serum and Plasma Specimens**

Ideally, the serum and plasma will be processed within 2 hrs from the time the blood is drawn to freezing when possible and must be frozen within 4 hrs of the blood draw. The faster the serum and plasma can be processed from blood draw to freezing the better. Serum and plasma processed within 1-2 hrs is the highest quality; serum and plasma processed within 2-4 hrs is a lower quality. Serum and plasma processed more than 4 hrs after drawing the blood is the poorest-quality serum and plasma for testing. Tracking the serum and plasma processing time is also critical in assessing specimen quality and suitability for testing.

Ideally, the serum and plasma will be frozen in an ultra-cold freezer (≤ -70ºC), in liquid nitrogen (liquid or vapor phase), or by direct exposure with excess dry ice. If ultra-cold freezing conditions are not available at your site, a non-cycling -20ºC freezer can be used; however, the amount of time the serum and plasma is kept in this type of freezer should be kept to a minimum because this temperature is not cold enough to achieve a frozen solid state (water-based liquids will be frozen solid at ≤ -56ºC). A non-cycling freezer is a freezer that will build up frost and requires defrosting by hand. Serum and plasma kept in a non-cycling -20ºC freezer should be surrounded with excess dry ice to allow the serum and plasma to achieve and then maintain a frozen solid state. Storage of serum and plasma in a frost-free -20ºC freezer will repeatedly damage the specimen each time the freezer cycles (that is, as the freezer thaws and then refreezes). Serum and plasma frozen under ultra-cold conditions represents the highest quality specimen suitable for all types of laboratory testing. Serum and plasma frozen in a non-cycling -20ºC provides a lower -quality specimens suitable for restricted types of laboratory testing. Serum and plasma frozen in a frost-free -20ºC freezer provides the lowest-quality specimens which has limited usefulness for research purposes. Tracking the freezing conditions for each serum and plasma specimen is of critical importance to assess specimen quality and suitability for testing.

**G. Instructions for Preparing Serum**

1. **Label Cryotubes**. Label the screw-cap cryotubes for each time point with the GOG protocol number, the GOG Bank ID, the Specimen Code and the collection date.
   * ***For GOG-0213, label ten 1.8 ml screw-cap with the GOG protocol number (GOG-0213), the GOG Bank ID (##-##-G###), the Specimen Code (SB01) and the collection date (mm/dd/yyyy)..***
2. **Draw Blood**. Draw 10 ml of blood into a **plain red-top** Vacutainer® tube not a serum separator tube.
3. **Allow Blood to Clot**. Allow the blood to **clot upright at room temperature for 30 minutes**.
   * ***If the blood cannot be centrifuged immediately (next step), store the clotted blood at 4ºC or in a bucket with excess wet ice for no longer than 3 hrs from the time of the blood draw. The faster the blood can be centrifuged after the 30 min clotting step, the better.***
4. **Centrifuge Blood**. Centrifuge the blood to separate the serum (clear straw-colored liquid) from the fibrin clot and the blood cells.
   * ***The optimal centrifugation conditions are ~3,500 x g at 4ºC for 10 min. The minimal centrifugation conditions are ~1000 x g at room temperature for 15 minutes. The longer centrifugation time compensates for the slower speed. Avoid centrifugations without refrigeration longer than 15 min because excess heat may build up in the unit and damage the serum.***

5. **Mix and Aliquot Serum**. Remove the caps from the blood tube, the 15 ml conical tube and the cryotubes. Transfer the serum into the 15 ml conical tube and gently mix the serum. Dispense (aliquot) the serum evenly into as many of the labeled screw-cap cryotubes as possible. Cap the cryogenic vials securely.
   * ***Fill each cryotube with a minimum of 0.25 ml (cc) to a maximum of 1.7 ml (cc) of serum. It is better to separate the serum into more cryotubes with a smaller volume than into fewer cryotubes with a larger volume.***
6. **Freeze Serum**. Freeze the serum in the cryotubes immediately in an upright position, when possible, using an appropriate type of freezing/storage space as described in section with guidelines and recommendations for preparing serum and plasma specimens.
7. **Complete the Form SP.** Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Include a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   * ***The type of storage condition prior to shipment (ultra-cold freezer/liquid nitrogen [$N_2$]/dry ice) and type of blood collection tube (red-top) must be specified on the specimen transmittal form (Form SP) for the serum specimen.***
8. **Ship the Serum**. Ship the frozen serum to the GOG Tissue Bank as described in Section IX.

**H. Instructions for Preparing Plasma**

1. **Label Cryotubes**. Label the screw-cap cryotubes for each time point with the GOG protocol number, the GOG Bank ID, the Specimen Code and the collection date.
   * ***For GOG-0213, label ten 1.8 ml screw-cap cryotubes with the GOG protocol number (GOG-0213), the GOG Bank ID (##-##-G###), the Specimen Code (PB01) and the collection date (mm/dd/yyyy).***
2. **Draw Blood**. Draw 10 ml of blood into a **purple-top (lavender-top)** Vacutainer® tube with the anticoagulant EDTA until the vacuum is exhausted**.**
3. **Allow Blood to Clot**. Mix the blood with the anticoagulant by **gently inverting the tube 5-10 times**.
   * ***If the next (centrifugation) step cannot be conducted immediately, store the blood at 4$^o$C in a refrigerator or in a bucket with excess wet ice for no longer than 3 hrs from the time of the blood draw. The faster the blood can be centrifuged after it is mixed with the anticoagulant the better.***
4. **Centrifuge Blood**. Centrifuge the blood to separate the plasma (clear straw-colored liquid) from the blood cells.
   * ***Ideally, centrifuge the blood at ~3,500 x g at 4$^o$C for 10 min. When the ideal equipment is not available, the minimum centrifugation requirements will be ~1000 x g at room temperature for 15 minutes. The longer centrifugation time will compensate for the slower speed. Avoid centrifugations without refrigeration longer than 15 min because excess heat may build up in the unit and damage the plasma.***
5. **Mix and Aliquot Plasma**. Remove the caps from the blood tube, the 15 ml conical tube and the cryotubes. Transfer the plasma into the 15 ml conical tube and gently mix the plasma. Dispense (aliquot) the plasma evenly into as many of the labeled screw-cap cryotubes as possible. Cap the cryogenic vials securely.
   * ***Fill each cryotube with a minimum of 0.25 ml (cc) to a maximum of 1.7 ml (cc) of plasma. It is better to separate the plasma into more cryotubes with a smaller volume than into fewer cryotubes with a larger volume.***
6. **Freeze Plasma**. Freeze the plasma in the cryotubes immediately in an upright position, when possible, using an appropriate type of freezing/storage space as described in section with guidelines and recommendations for preparing serum and plasma specimens.
7. **Complete the Form SP.** Complete a GOG Specimen Form (Form SP) as specified in Section VIII. Include a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   * ***The type of storage condition prior to shipment (ultra-cold freezer/liquid nitrogen [$N_2$]/dry ice) and type of blood collection tube (EDTA) must be specified on the specimen transmittal form (Form SP) for the plasma specimen.***

8. **Ship the Plasma to the GOG Tissue Bank**. Ship the frozen plasma to the GOG Tissue Bank as described in Section IX.

# VII. Preparing Whole Blood for GOG-0213

## A. Requirement

An amendment has been approved to collect a whole blood specimen from new patients on GOG-0213 as well as women who have already been enrolled on GOG-0213 regardless of randomization and treatment. Patients already enrolled on GOG-0213 will need to be re-consented. Blood must only be collected from women who give permission for their blood to be submitted and used for this research study.

If the patient gives permission, 10 ml blood will need to be drawn into a purple-top Vacutainer® tubes with the anti-coagulant EDTA at one time point. The whole blood will need to be collected as described in Section VII-D and shipped to the GOG Tissue Bank as described in Section IX.

Patients may participate in this treatment protocol even if they don't give permission for their blood to be used for research or if the submitting institution is a Non-US site and submission of blood is logistically infeasible. **If blood cannot be submitted for GOG-0213, please indicate the reason in item 5 on the SP Form, such as patient refused, tried but not able to draw blood, or Non-US site logistically infeasible.**

## B. Time Point

Whole blood will need to be collected prior to or after starting treatment on this phase III trial or at any time during follow up. Although the collection time point is flexible, we encourage sites to try and collect the blood as soon as possible to remove this requirement from your patient's form schedule. If you need to get an extension for submitting the whole blood specimen, please contact a Translational Research Scientist at 716-845-5702.

## C. Purpose

The translational research objective of this protocol is to bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.

## D. Instructions for Preparing Whole Blood

1. **Label the Purple-Top Vacutainer® Tube.** Label the 10-ml Purple-Top Vacutainer® tube with EDTA for this protocol with the GOG protocol number (GOG-0213), GOG Bank ID Number (####-##-G###), the Specimen Code (WB01 for whole blood), and the collection date (mm/dd/yyyy).
2. **Draw Blood**. Draw 10 ml of blood into the Purple-Top Vacutainer® tube with EDTA until the vacuum is exhausted**.**
   *** For GOG-0213, do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood.
3. **Mix Blood with the EDTA**. Mix the blood with the anticoagulant (EDTA) by gently inverting the tube 5-10 times.
4. **Store the Blood at Room Temperature.** Store the blood at room temperature until the specimen can be shipped to the GOG Tissue Bank.
5. **Complete the Form SP**. Complete the GOG Specimen Form (Form SP) online using SEDES as specified in Section VIII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   * ***Please remember to indicate the Specimen Type is "Whole blood" in item 8, the Items Shipped is "Tube/Vial" in item 9, the quantity shipped is "1" in Item 10, the "Storage Type" is "Room Temperature", the "Type of blood collection tube" is "EDTA", and "Platelet count required" is "No".***

6. **Ship the Blood.** Ship the blood for a given GOG-0213 patient the day the blood is drawn to the GOG Tissue Bank as described in Section IX.
   * ***Please note that the blood specimen must be shipped the day the blood is drawn for delivery the next morning as this specimen must undergo immediate processing upon receipt to extract high quality DNA.***

# VIII. Submitting Form SP for GOG-0213

### A. Form SP Requirements for Each GOG-0213 Patient

One Form SP must be completed and electronically submitted to the GOG Statistical and Data Center (SDC) ***for each specimen*** required for the protocol regardless of the specimen submission status using the SDC Electronic Data Entry System (SEDES). Specific instructions for completing Form SP are available via SEDES by scrolling down to the SP Forms for GOG-0213.

### B. Instructions for Submitting Form SP Online

Form SP must be submitted to the GOG SDC online using SEDES which is available on the GOG Web Menu under *Registration/Data Entry*. To access Form SP for online submission, log onto the GOG Web Menu and use SEDES to electronically enter Form SP data. Any questions about access or problems should be directed to the User Support Department at the GOG Statistical and Data Center at support@gogstats.org or by phoning 716-845-7767. Retain a printout of the completed form for your records and include a copy of the completed form when the specimen is shipped to the GOG Tissue Bank. It is not necessary to send a completed Form SP to the GOG Tissue Bank when the specimens are not submitted.

# IX. Shipping Specimens for GOG-0213

**A. All** specimens will be shipped to the GOG Tissue Bank at the following address:

**GOG Tissue Bank – Protocol GOG-0213**
**Nationwide Children's Hospital**
**700 Children's Drive, WA1340**
**Columbus, OH 43205**
**Phone: (614) 722-2865**
**Fax: (614) 722-2897**
**E-mail:** gogbank@nationwidechildrens.org

### B. Archival Primary or Metastatic Tumor - Block or Sections (Mandatory Specimen)

An archival primary or metastatic tumor specimen (FT01) either a block or unstained sections must be shipped to the GOG Tissue Bank within 8 weeks of study enrollment **using your own shipping container** at the address provided using the US Postal Mail at your own expense. If shipping slides, please pack slides in a plastic slide cassette labeled with the GOG protocol code, Bank ID, specimen code and collection date. Tape the slide cassette shut and wrap in bubble wrap in bubble wrap or another type of padded material before shipment. This specimen may also be included in the dual chamber Specimen Kit for GOG-0213 if it was available when the recurrent tumor, pre-op serum and/or normal tissue are ready to be shipped to the GOG Tissue Bank.

### C. Fixed Recurrent Tumor and Frozen Recurrent (Mandatory Specimens) as well as the Pre-Op Serum, Pre-Op Plasma, Formalin-Fixed Normal Tissue and Frozen Normal Tissue (Optional but High Priority Specimens)

To satisfy the specimen requirement(s) for patients who are enrolled at GOG or CTSU Institutions, are randomized to have secondary cytoreductive surgery and give permission for their serum and/or tissue to be used for this research study, the mandatory fixed recurrent tumor (FR01) and frozen recurrent tumor (RR01) specimens and any of the optional specimens (pre-op serum – SB01, pre-op plasma – PB01, fixed normal tissue – FN01 and frozen normal tissue – RN01) will need to be shipped to the GOG Tissue Bank **using the dual-chamber Specimen Kit** within 3 days of surgery when possible. If this is not possible, please ship them to the GOG Tissue Bank at your earliest convenience. The SP Forms for these specimens, however, must be received at the GOG Statistical and Data Center within 7 days of surgery.

**Instructions for Shipping Fixed and Frozen Specimens**

1. **Bag the Fixed Tissue Specimens.** Transfer the fixed recurrent tumor and/or normal tissue in a jar(s) of formalin or embedded in a paraffin block(s) into a plastic biohazard secondary envelope containing absorbent material, and then put the secondary envelope into the Tyvek envelope. Expel as much air as possible before sealing both envelopes.
2. **Pack the Fixed Tissue Specimens into the Kit.** Place the Tyvek envelope containing the fixed tissue specimens into one chamber of the Dual-Chamber Specimen Kit.
3. **Pre-Fill Kit with Dry Ice.** Layer dry ice into the other chamber of the Dual-Chamber Specimen Kit until it is about 1/3 full.
4. **Transfer Frozen Specimens into Individual Zip-Lock Bags.** Transfer the frozen recurrent tumor, frozen normal tissue, cryotubes of frozen serum and/or cryotubes of frozen plasma from each patient into individual zip-lock bags. Expel as much air as possible before sealing the bag.
5. **Transfer the Bags of Frozen Specimens into a Secondary Envelope and a Tyvek Envelope.** Transfer the zip-lock bags with the frozen recurrent tumor tissue, frozen normal tissue, the cryotubes of frozen serum and/or the cryotubes of frozen plasma into a plastic biohazard secondary envelope containing absorbent material, and then put the secondary envelope into the Tyvek envelope. Expel as much air as possible before sealing both envelopes.
6. **Pack Specimens and Dry Ice into the Specimen Kit .** Place the Tyvek envelope containing the frozen specimens into the chamber and then fill the kit to the top with dry ice.
7. **Insert SP Forms.** Insert a copy of the SP Forms for each specimen packed in this Specimen Kit in the space between internal chambers and the outside plastic holder.
8. **Seal Kit Securely.** Place the styrofoam cover on top of the Kit and then seal the kit securely with filament or other durable sealing tape.
9. **Print and Attach Shipping Label**. Access the GOG Tissue Bank's Kit Management application via the GOG Web Menu to obtain a shipping label. Once in the application select "Shipping Label" from the tool bar at the top of the screen in order to print a Federal Express shipping label.
10. **Complete and Attach Other Labels**. After completing the Dry Ice Label (UN1845), attach the Dry Ice Label and an Exempt Human Specimen Sticker to the side of the box.
11. **Arrange for Pick-Up**. Make arrangements for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355.
12. **Ship Specimens.** Ship the fixed and frozen specimens with the accompanying SP Forms to the GOG Tissue Ban k via Federal Express Priority Overnight delivery Please ship specimens Monday through Thursday for a Tuesday through Friday delivery.

## D. Submission of Whole Blood for GOG-0213.

A whole blood specimen will be required for all patients who give permission for their blood to be submitted and used for this research study.

Although the GOG Tissue Bank will not provide a specimen kit for shipping this whole blood specimens to the GOG Tissue Bank for GOG-0213, your institution will still be required to comply with International Air Transportation Association (IATA) standards (www.iata.org).

To ship whole blood specimens to the GOG Tissue Bank at ambient temperature you will need the following: (1) sturdy shipping container (e.g., a FedEx Box or another type of cardboard or Styrofoam

box), (2) biohazard bag with absorbent material, (3) puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) Exempt Human Specimen Sticker, and (5) blank *FedEx Express US Airbill*.

If you do not have these materials available at your Institution, you may order them from any supplier.

Biohazard bag and absorbent material can be ordered from Saf-T-Pak (Phone: 800-814-7484; Website: www.saftpak.com).

- STP-710 Disposable 2-Part Secondary Pressure Vessel, Medium (i.e., secondary shipping envelope)
- STP-151 100 mL Absorbent Strip – 6 inches (i.e., absorbent material)

Cardboard FedEx shipping boxes are available from FedEx at no charge. If you do not have a FedEx pick-up and supply center at your Institution, you can request that your Driver bring extra boxes to you at your next pick-up. FedEx Customer Service can be reached at 800-Go-FedEx (800-463-3339).

If your Institution has a small number of patients on GOG trials or has limited funding to purchase supplies, please consider "cost sharing" with other GOG institutions or your parent institution.

**Instructions for Shipping Whole Blood Specimens For DNA Extraction Using Your Own Shipping Container**

***Special reminder*:** The whole blood specimens for this protocol must be shipped to the GOG Tissue Bank at ambient (room) temperature the day the blood is drawn. These blood specimens must be drawn in a 10-ml purple-top (EDTA) tube and can be shipped on a Monday through Friday schedule for Tuesday through Saturday morning delivery. Bank staff will be available for immediate processing of the blood specimens upon receipt. Bank staff do not work holidays and will not be available to process the blood so d**o not collect blood for GOG-0213 the day before a holiday.** Please make other arrangements to collect this blood specimen on a different day. **Please note that you can place up to 4 different blood specimens in one biohazard bag.**

1. **Place the Whole Blood Tube(s) into a Biohazard Bag with Absorbent Material.** Place the whole blood specimen labeled with the protocol code, Bank ID, specimen code (WB01) and collection data into a biohazard bag with an absorbent strip. Expel as much air as possible before sealing the bag.
2. **Place the Blood Tube(s) into a Tyvek Envelope.** Next place the blood wrapped in padding into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
3. **Place the Tyvek Envelope into a Sturdy Cardboard Box and include Bubble Wrap or Other Padding as Needed.** Place the Tyvek envelope containing up to 4 whole blood specimens into a sturdy cardboard box like the smallest cardboard FedEx box. If you are using a larger cardboard box, you can batch ship blood in more than one Tyvek envelope each containing up to 4 tubes of blood. Include bubble wrap or other padding as needed to secure the Tyvek envelope(s) inside the box.
4. **Place the SP Form(s) into the Cardboard Box.** Insert a print out of the SP Form(s) for the whole blood specimen(s) into the cardboard box.
5. **Tape the Cardboard Box.** Seal the cardboard box with filament or other durable sealing tape.
6. **Print and Attach a Shipping Label.** Access the GOG Tissue Bank's Kit Management application via the GOG Web Menu to obtain a shipping label. Once in the application select "Shipping Label" from the tool bar at the top of the screen in order to print a Federal Express shipping label. If blood is collected on a Friday, please select "*Saturday Delivery"*. Saturday delivery is **only available** for the shipment of whole blood.
7. **Complete and Attach Other Labels.** Attach the Exempt Human Specimen Sticker to the side of the cardboard box.
8. **Arrange for Federal Express Pick-Up.** Make arrangements for Federal Express pick-up through your usual institution procedure or by calling 1-800-238-5355.

9. **Ship the Specimens to the GOG Tissue Bank.** Ship the whole blood specimen(s) and the SP Form(s) at ambient temperature to the GOG Tissue Bank at the address provided above on a Monday through Friday schedule for a Tuesday through Saturday morning delivery.

# X. Banking Specimens for GOG-0213

The GOG Tissue Bank staff will be responsible for all of the general activities associated with receiving, banking and distributing the clinical specimens submitted for GOG-0213. The Bank staff will also be responsible for preparing and distributing Dual-Chamber Specimen Kits with the materials specified in Section III for this protocol. The cost of shipping the GOG-0213 specimens from the GOG participating institutions to the GOG Tissue Bank will be billed to the GOG Tissue Bank Federal Express account.

Upon receipt of any shipments containing specimens for GOG-0213, the GOG Tissue Bank staff will immediately assess the type, quantity, and condition of the specimens received; complete the appropriate fields in the GOG Specimen Form; enter the specimens into their database system; and store the specimens under the appropriate conditions. The GOG Tissue Bank staff will complete the bottom part of Form SP for each specimen and submit the data to the GOG Statistical and Data Center electronically within 3 business days of receiving any clinical specimens for this protocol. A copy of the completed Form SP for each specimen will be retained in the files kept at the GOG Tissue Bank. In addition, the GOG Tissue Bank will work with the GOG Statistical and Data Center to reconcile specimen identifiers, information, condition, and quality as needed.

### A. Archival Formalin-Fixed and Paraffin-Embedded Tumor and Normal Tissue

Archival or formalin-fixed tissue will be received as a paraffin block, sections (sixteen unstained sections, 5 micrometer in thickness, on charged slides suitable for standard immunohistochemistry assays) or in a formalin-jar. Staff at the GOG Tissue Bank will make sure that each block, slide or formalin-jar is labeled with the GOG protocol number (GOG-0213), GOG Bank ID, the appropriate specimen code and the collection date. FT01 will be used for archival primary or metastatic tumor. If both are submitted, ideally FT01 will be used for archival primary tumor and FT02 will be used for archival metastatic tumor. If this is not the case, the staff at the GOG Tissue Bank should not relabel these specimens. Formalin-fixed recurrent tumor should be labeled with the specimen code FR01 whereas formalin-fixed normal tissue should be labeled with the specimen code FN01. When research specimens undergo pathology review, if the type of tissue in the research specimen does not match up with the electronic data in item 22 on the SP Form (type of tissue), staff at the GOG Tissue Bank will need to inform the GOG Statistical and Data Center and the GOG Institution so that item 22 on Form SP can be amended.

1. **Block**. If a paraffin block is received, each block will be stored under vacuum and protected from light until sections need to be prepared and/or blocks need to be cored to prepare tissue microarrays (TMAs) for this protocol.

   a. **Unstained Sections**.

      Just before distribution of these specimens for laboratory testing, sections will be prepared as needed based on the type of testing to be performed. Individual slides will be labeled with the identifiers indicated above. The slides will then distributed wax-dipped, stored under vacuum, and protected from light.

   b. **Tissue Microarrays (TMAs)**.
      The GOG Tissue Bank will collaborate with the GOG Statistical and Data Center and the GOG Tissue Utilization Subcommittee to design and create a series of TMAs for GOG-0213 to study markers of recurrence, survival and treatment response or resistance. The specific types of the TMAs that can be created will depend on the paraffin block submissions for this protocol and the clinical outcomes observed for these cases. For example, one TMA could contain matched cores

of tumor collected prior to initiating first line and second-line therapy with adjacent normal tissue from secondary cytoreductive surgery whereas another TMA could represent tumor cores from patients who experienced short survival, intermediate survival or long survival or include tumor cores from patients treated on a specific treatment arm who experienced short, intermediate or long progression-free survival. Ideally, each TMA will contain 250 cores with 200 individual cases and 50 controls. Since three to four cores from the same paraffin block are needed to reflect staining in a conventional tissue section, each of GOG-0213 TMAs will be generated in quadruplicate. Each quadruplicate TMA block will contain 200 independent cases with the same 50 controls. This will allow one set to be used for screening or exploratory analyses and the other for validation. The controls will include: 15 human cell lines with known molecular profiles, 20 gynecologic tissues [normal and cancer], and 15 non-gynecologic tissue [normal and cancer]. Incorporation of the same controls on each of these TMAs will allow investigators to evaluate the performance of the individual arrays and allow inferences to be drawn across arrays when certain criteria are satisfied. The Bank will position the cores in fixed positions in the quadruplicate blocks. Each core will be 1 mm in diameter and 2 mm in depth whenever possible. In cases where lesion size is a limitation, 0.8 mm x 2 mm cores will be obtained. Core loss during sectioning will increase with the number of sections into the block and statistical sections will build in an average estimated loss of 15%. GOG pathologists will identify the highest quality cases for inclusion on the TMA, select the exact sites within a block to be cored for the TMA, and evaluate the quality of the TMA sections generated including a light microscopic examination of core integrity and loss as well as neoplastic cellularity. Immunohistochemical staining for markers that are sensitive to fixation conditions and oxidation including p27 and androgen receptor may be used to identify tissues suitable for coring. Each TMA section will be wax dipped, vacuum sealed and protected from light to protect the antigenicity of the tissue prior to distribution for laboratory testing.

2. **Unstained Sections**. When tissue specimens are received as unstained sections, the slides will be wax-dipped, stored under vacuum, and protected from light.

3. **Pieces of Tissue in a Formalin-Jar**. When tissue specimens are received in a formalin-jar, the tissue will undergo standard histologic processing and be embedded in a paraffin block. The blocks will be stored under vacuum, and protected from light until sections need to be prepared and/or blocks need to be cored to prepare tissue microarrays (TMAs) for this protocol.

**B. Frozen Recurrent Tumor and Normal Tissue Specimens**

Frozen recurrent tumor and normal tissue will be received snap frozen or OCT-embedded and frozen. Staff at the GOG Tissue Bank will make sure the tumor specimen (actually the zip-lock bag and/or the OCT mold) is labeled with the GOG protocol number (GOG-0213), GOG Bank ID, the appropriate specimen code (RR01 for recurrent tumor and RN01 for normal tissue) and the collection date. The frozen tissue specimen will be stored at the Bank in an ultra-cold freezer (≤ -70$^{o}$C) or in a liquid nitrogen storage tank.

**C. Pre-Op Serum**

Frozen pre-op serum will be received as aliquots in up to 10 screw-cap cryogenic vials. Staff at the GOG Tissue Bank will make sure that each aliquot of pre-op serum is labeled with the GOG protocol number (GOG-0213), GOG Bank ID, the appropriate specimen code (SB01) and the collection date. These aliquots will be stored at the Bank in an ultra-cold freezer (≤ -70$^{o}$C) or in a liquid nitrogen storage tank. In order for serum to be considered as satisfactory for GOG-0213, the processing time in Item 11 on Form SP should be "< 4 hours", the type of storage condition in Item 12 on Form SP should be "Ultracold freezer/liquidN2/dry ice", the type of type of blood collection in Item 16 on the SP Form should be "Red top", and the serum should arrive at the Bank frozen solid in contact with visible dry ice.

**D. Pre-Op Plasma**

Frozen pre-op plasma will be received as aliquots in up to 10 screw-cap cryogenic vials. Staff at the GOG Tissue Bank will make sure that each aliquot of pre-op plasma is labeled with the GOG protocol number

(GOG-0213), GOG Bank ID, the appropriate specimen code (PB01) and the collection date. These aliquots will be stored at the Bank in an ultra-cold freezer (≤ -70ºC) or in a liquid nitrogen storage tank. In order for plasma to be considered as satisfactory for GOG-0213, the processing time in Item 11 on Form SP should be "< 4 hours", the type of storage condition in Item 12 on Form SP should be "Ultracold freezer/liquidN2/dry ice", the type of type of blood collection in Item 16 on the SP Form should be "EDTA", and the plasma should arrive at the Bank frozen solid in contact with visible dry ice.

**E. Whole Blood**

Each whole blood specimen will need to be processed immediately upon receipt to extract DNA, assess the DNA concentration and quality, and then to store the DNA in an ultra-cold freezer in aliquots labeled with the GOG protocol code, Bank ID, specimen code (WB01-DNA) and collection date. Ideally the blood will be received in a liquid state in a purple-top Vacutainer® tube with EDTA. Staff at the GOG Tissue Bank will need to document the date of DNA extraction using the format mm/dd/yyyy, DNA concentration in [brackets] and 260/280 ratio in (parenthesis) in item 30 on Form SP and to note comments regarding specimen condition in item 31 on Form SP.

# XI. Distributing Specimens for Laboratory Testing for GOG-0213

Chairs of the GOG Committee for Experimental Medicine and the GOG Tissue Utilization Subcommittee will coordinate to make decisions regarding when specimens will be distributed to approved-investigators for approved laboratory testing. The GOG Statistical and Data Center and the GOG Tissue Bank will work together to coordinate the physical distribution of the specific specimens for select patients to the approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information.

For each shipment, the GOG Tissue Bank staff will need to e-mail the investigator and the GOG Statistical and Data Center an electronic file that includes an inventory of all specimens included in the shipment with the specimen specific identifiers as well as quantity and condition of the specimens being shipped. The GOG Statistical and Data Center will email the investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data. The investigator will need to use the specimen identifiers in the electronic file from the GOG Statistical and Data Center to avoid having to enter these identifiers thus reducing redundant data entry and minimizing the chance for errors when connecting the laboratory testing data to the clinical information for the GOG participating institutions.

The investigators performing the laboratory testing on any GOG-0213 specimens will not be given access to any personal identifiers. The investigators will be responsible for the direct supervision and oversight of the laboratory testing performed on these specimens. The individuals at the respective laboratories will be responsible for keeping accurate records of all laboratory testing performed on the GOG-0213 specimens, ensuring that the laboratory testing results are linked to the appropriate specimen-specific identifiers and transferring relevant laboratory data to the GOG Statistical and Data Center for analysis. The study chair will coordinate with the study co-chairs, scientific collaborators and the GOG Statistical and Data Center to analyze, report, and publish the study results.

**A. Archival and Formalin-Fixed Tissue Specimens (Primary, Metastatic and/or Recurrent Tumor as well as Adjacent Normal Tissue)**

When appropriate, the GOG Tissue Bank staff will be responsible for shipping a specified number of unstained sections from conventional paraffin blocks and/or the GOG-0213 TMAs to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker, proteomic and genomic analyses. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in this specimen will be reevaluated based on evolving data in the field.

**B. Frozen Recurrent Tumor and Normal Tissue**

When appropriate, the GOG Tissue Bank staff will be responsible for shipping a specific quantity of frozen tumor tissue, frozen sections and/or scrolls from select GOG-0213 patients to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker, proteomic and genomic analyses. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in these specimens will be reevaluated based on evolving data in the field.

**C. Pre-Op Serum and Pre-Op Plasma**

When appropriate, the GOG Tissue Bank staff will be responsible for shipping an aliquot of satisfactory pre-op serum and pre-op plasma from select GOG-0213 patients to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for biomarker and proteomic analyses. The exact choice of the biomarkers and proteomic profiles to be evaluated and the assays to be performed in these specimens will be reevaluated based on evolving data in the field.

D. **DNA from Whole Blood**

When appropriate, the GOG Tissue Bank staff will be responsible for shipping an appropriate quantity of DNA with corresponding Q/C data to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for whole genome SNP-associations studies and/or evaluation of individual SNPs.

# XII. Distributing Specimens for Future Research

All of the residual tumor, tissue, serum and plasma specimens still remaining after completion of GOG-0213 and any whole blood collected from women on GOG-0213 will be banked in the GOG Tissue Bank and made available as needed for approved cancer or non-cancer research projects based on GOG Tissue Bank - Specimen Distribution Policies if the following condition is satisfied: Each study patient in question must have provided permission for the use of her specimens for cancer and/or non-cancer research. These responses (choices) will be documented on the informed consent document that the patient signs for the protocol and electronically when the staff at the treating GOG institution enters the patient's choices online using the Specimen Consent Application available on the GOG website.

The Specimen Consent Application also captures the patient's decision regarding (1) the use of her clinical information collected by the GOG as part of her participation in this trial for future research that uses her specimens, (2) the use of her specimens to be used for future research to study changes in genetic material (those passed on in families or that are not passed on in families but are either natural changes or influenced by environment and lifestyle), and (3) for someone at your institution such as a doctor or nurse to contact her in the future to ask her to take part in more research.

**The specimens will be used for research purposes only until they are used up or until the patient changes her mind.** The staff at the GOG treating institutions will use the Specimen Consent Application to amend the patient's choice(s) regarding the future use of her specimens if the patient changes her mind. This application

shares information with the GOG Statistical and Data Center and the GOG Tissue Bank and has management, reporting, confirmation and validation features. If the patient does not give permission for the use of her specimens for future cancer or non-cancer research, the GOG Tissue Bank will be instructed to destroy (incinerate) any remaining specimens to insure that the patient's wishes are honored.

Chairs of the GOG Committee for Experimental Medicine and the GOG Tissue Utilization Subcommittee will coordinate to make decisions regarding when specimens will be distributed to approved investigators for approved laboratory testing. The GOG Statistical and Data Center and the GOG Tissue Bank will work together to coordinate the physical distribution of the specific specimens for select patients to the approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information. The GOG Statistical and Data Center will email the investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data if appropriate. For each shipment, the GOG Tissue Bank staff will e-mail the investigator and the GOG Statistical and Data Center an electronic file that includes an inventory of all specimens included in the shipment with the specimen specific identifiers as well as quantity and condition of the specimens being shipped.

The investigators performing approved research on any GOG-0213 specimens will not be given access to any personal identifiers. The investigators will be responsible for the direct supervision and oversight of the laboratory testing performed on these specimens. The individuals at the respective laboratories will be responsible for keeping accurate records of all laboratory testing performed in the GOG specimens, ensuring that the laboratory testing results are linked to the appropriate specimen-specific identifiers and transferring relevant laboratory data to the GOG Statistical and Data Center for analysis. The approved principal investigator (PI) will coordinate with co-PIs, scientific collaborators and the GOG Statistical and Data Center to analyze, report, and publish the research results. Any presentation or publication will comply with the GOG Publications Policy and acknowledge the National Cancer Institute grants to the GOG Administrative Office (CA 27469), the GOG Tissue Bank (CA 27469 and CA 11479) and the GOG Statistical and Data Center (CA 37517).

APPENDIX IV

**NCI Standard Protocol Language (as of March 26, 1998) Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA):**

The agents (hereinafter referred to as "Agent"), **Bevacizumab and Erlotinib**, used in this protocol are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between **Genentech, Inc.** (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment, Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):

a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time (see #5). Clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX: (301) 402-1584

The Regulatory Affairs Branch will then distribute them to the Collaborator.

# APPENDIX V

## CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.

3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to "non-IDMS" conversion) is also available, if needed for dose modifications (see below).

**Dosing of Carboplatin:**

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3) Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

4) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

5) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

**Maximum** carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

**The maximum allowed doses of carboplatin are:**

**AUC 6 = 900 mg**

**AUC 5 = 750 mg**

**AUC 4 = 600 mg**

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):

    a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
    b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
    c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
    d. Adjusted weight calculation:
    Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5

    **Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight**

    e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

**At the time of a dose modification for toxicity:**

1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

## 11.0 STATISTICAL CONSIDERATIONS - **ORIGINAL Statistical Analysis Plan**

### 11.1 **Randomization**

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies:

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 **CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment (CTB).

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.13 No cytoreductive surgery

11.14 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments. For those who consent to have cytoreductive surgery determined through randomization, the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study.

### 11.2 **Measures of Efficacy and safety**

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

### 11.3 **Treatment efficacy**

*Overall type I error:* This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

*Expected median survival on the standard treatment:* Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

*Accrual target for evaluating the efficacy of systemic therapy*
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

*Statistical power for evaluating the efficacy of biologic therapy*: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: $H_{01}$: $\Delta_{01} = \lambda_{CTB} / \lambda_{CT} \geq 1$ will be assessed, where $\lambda_{\cdot}$ is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their assigned treatment. The type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months).

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve

for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

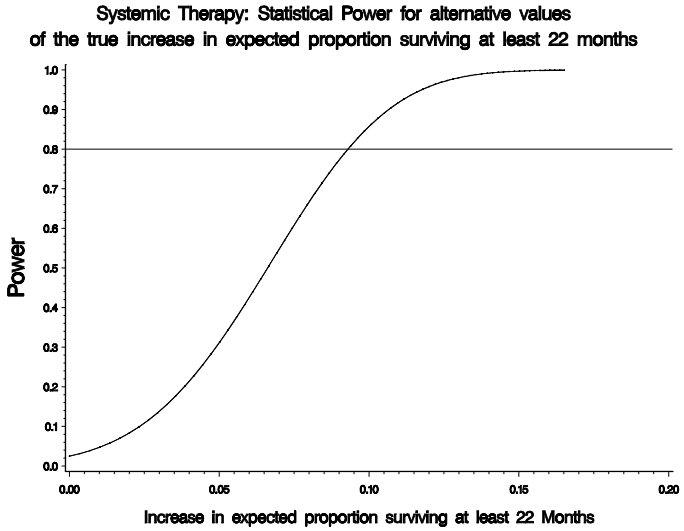


**Figure 1.**

*Statistical Power- evaluating the efficacy of surgical cytoreduction*: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival ($H_{02:}\ \Delta_{02} = \lambda_{\text{surgery}} / \lambda_{\text{No surgery}} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment assignment (CT vs CTB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12 months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses.

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, $H_{02,}$ when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2.

The proportion of patients enrolled onto this study, who will be candidates for surgical cytoreduction and consent to having their surgical intervention determined by randomization, is unknown. If 50% of all enrolled patients

participate in the surgical component of this study then there will be approximately 214 deaths reported in this subset of patients (660*0.50*0.65, assuming surgery has no effect on overall survival) when the study is considered sufficiently mature for a final analysis of the systemic therapies (objective 1). On the other hand, if only 30% participate in the surgical component of this study then the expected number of deaths reported at this time will be 129.

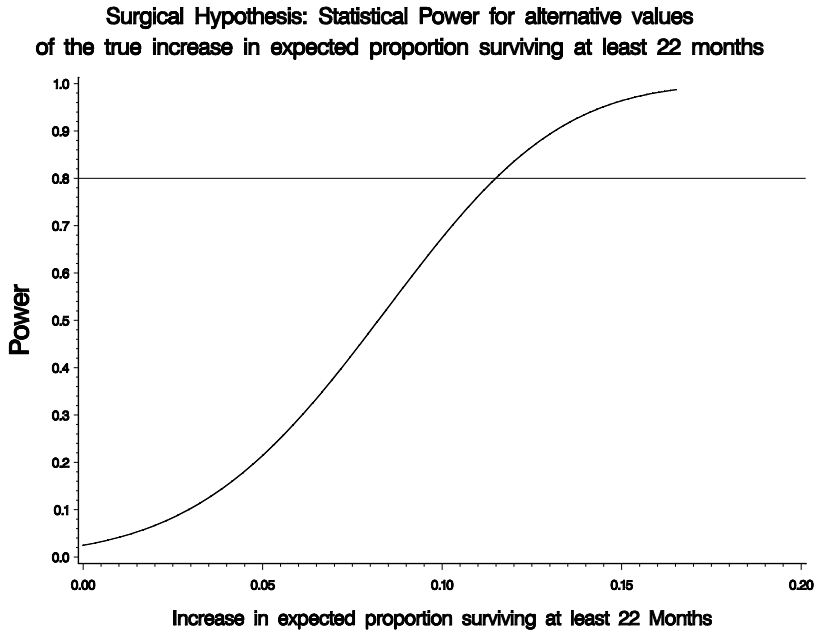


**Figure 2.**

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin (ARM 1). It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.

*Interim Analyses:* Interim analyses are planned when there are at least 110 deaths reported among all those patients allocated to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and July each year and the precise date of these meetings is set without confidential knowledge of the study results.

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information time, $H_{01}$ will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis.

$H_{02}$ will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of $H_{02}$ will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for $H_{01}$ (or $H_{02}$) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $\Delta_{01} > 1.0$ (or $\Delta_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%.

The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization

to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

*Final analysis:* The study will be considered sufficiently mature to permit a final assessment of $H_{01}$ when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of $H_{02}$ when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

*Supplemental final analyses:* A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

*Safety Analyses:* The GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities, serious adverse event (SAE) reports and deaths in which study treatment may have been a contributing cause. This committee does not review efficacy results. The DSMB may recommend study amendments pertaining to patient safety.

Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash

and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

## 11.4 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

*Construct and content*

The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items) [43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

*Descriptive analyses of baseline QOL scores*

Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean,

standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

*Differences in FACT-TOI scores between patients receiving CT and CTB:* Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

*Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:*

This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

*Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery.* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

## 11.5 Translational Research Statistical Considerations

*Overview*

The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

*Anticipated sample size for translational objectives*

The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately

198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1. Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

*Training and validation set*
In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.

*Identifying biologic/molecular profiles*
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

*Reliability*
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which can not be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify

which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

*Validation*

Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is know to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators,

since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.6 The anticipated distribution of patients' race and ethnicity for the systemic therapy portion of this trial is (all are female):

| | |
|---|---|
| White (not Hispanic) | 584 |
| Black (not Hispanic) | 39 |
| Hispanic | 14 |
| Asian | 17 |
| American Indian or Alaskan Native | 3 |
| Native Hawaiian or other Pacific Islander | 3 |

11.1 STATISTICAL CONSIDERATIONS - **Statistical Analysis Plan at the time of OB1 Analysis**

11.2 Randomization**(10/01/12)**

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies: (All patients enrolled after August 28, 2011 will have their surgical cytoreductive treatment determined through randomization. These patients will select one of the following systemic treatments and declare their selection prior to enrollment onto the study) **(08/29/11)(12/19/11)**

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 GC: A standard regimen consisting of carboplatin (AUC 4) day 1 and gemcitabine (1000 mg/$m^2$) day 1 and 8 for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.13**CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment.

11.14 GCB: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until toxicity or progression necessitates discontinuing treatment early.

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.15 No cytoreductive surgery

11.16 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments (this sentence applies only to patients enrolled prior to Aug 29, 2011, thereafter patients select either CT, GC, GCB or CTB as their systemic treatment.). For those who consent to have cytoreductive surgery determined through randomization,

the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study.**(08/29/11)**

11.3 Measures of Efficacy and safety

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

11.4 Treatment efficacy

*Overall type I error:* This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

*Expected median survival on the standard treatment:* Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

*Accrual target for evaluating the efficacy of systemic therapy*
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

*Statistical power for evaluating the efficacy of biologic therapy*: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: $H_{01}: D_{01} = l_{CTB} / l_{CT} \geq 1$ will be assessed, where $l$ is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their randomly assigned treatment. This comparison will not include those patients who were enrolled after August 28, 2011 and hence selected their systemic treatment. The

type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months).**(08/29/11)(12/19/11)**

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

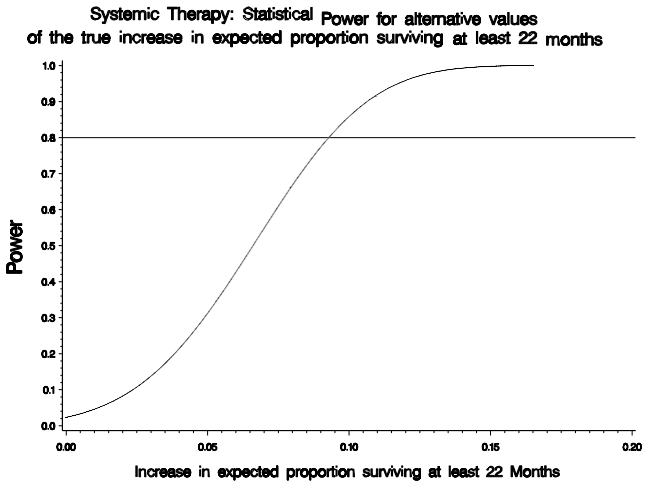


**Figure 1.**

*Statistical Power- evaluating the efficacy of surgical cytoreduction*: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival ($H_{02}$: $D_{02} = l_{surgery} / l_{No\ surgery} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their randomly assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment (CT vs CTB vs. CG vs CGB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12

months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses. **(08/29/11)(10/01/12)**

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, $H_{02,}$ when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2. The anticipated total accrual for this component of the study is 360 patients.**(08/29/11)**

*An addendum to the statistical considerations following the amendment to extend recruitment to the surgical component of the study.* ***(12/19/2011)***

As of Nov-1-2011, there were 114 patients enrolled onto the surgical component of this study and 17 of these patients had died. The planned total number of patients to be enrolled onto the surgical component of this study is 360 patients. There were 35 patient enrolled during 2010, and 34 patients are projected to be enrolled during 2011. Therefore, assuming the future accrual is 35 patients per year, this study is expected to complete its targeted accrual in 7 years (Nov-2018). Patients enrolled after Aug-28-2011 will have their cytoreductive surgery determined by randomization. All of these patients will receive a standard carboplatin-paclitaxel regimen and permitted to choose whether to have bevacizumab supplement their treatment.

The data currently available from GOG-0213, indicates that the marginal hazard of death is approximately 0.021 $month^{-1}$. Assuming a constant hazard, the expected number of deaths when the accrual is completed among the 114 patients, who are already enrolled onto the surgical component of this study is 97.4. Assuming a similar death rate for all future patients, Simpson's rule (Schoenfeld, Biometrics 1983) can be used to estimate the number of patients among those who will be enrolled over the next 7 years and will have died when the accrual has been completed (130.1 deaths). Hence the expected total number deaths at the time when the target accrual is completed is 97.4+130.1 = 227.5. Likewise, the expected number of deaths reported 9 months after the targeted accrual is complete is 100.2+150.0=250.2, which is approximately the number required for the final analysis.

Therefore, the targeted date for completing the accrual to the surgical component of this study is Fall-2018. The required number of deaths required for the final analysis (250 deaths) is expected to occur nearly 1 year after the targeted accrual has been completed. In the event that the required number of deaths for the final analysis is observed before the targeted accrual is completed, then accrual will be stopped prior to attaining the targeted accrual. The planned analyses and the

power calculations provided above are unchanged by this revised recruitment plan.**(12/19/2011)**

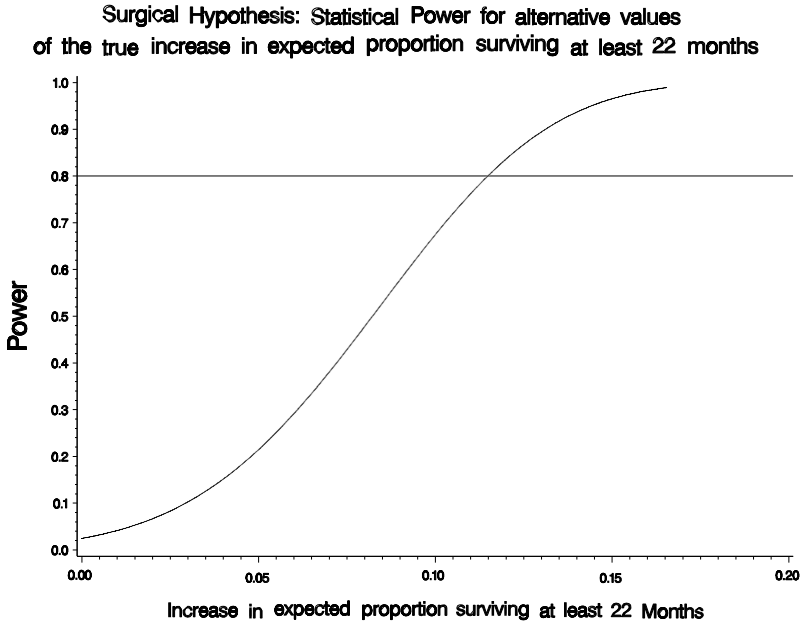


**Figure 2.**

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin with or without bevacizumab. It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.**(08/29/11)**

*Interim Analyses:* Interim analyses are planned when there are at least 110 deaths reported among all those patients randomly allocated (prior to August 29, 2011) to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and

July each year and the precise date of these meetings is set without confidential knowledge of the study results. **(10/01/12)**

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those randomly allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information time, $H_{01}$ will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis. **(08/29/11)**

$H_{02}$ will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of $H_{02}$ will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for $H_{01}$ (or $H_{02}$) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $D_{01} > 1.0$ (or $D_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%. The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

*Final analysis:* The study will be considered sufficiently mature to permit a final assessment of $H_{01}$ when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of $H_{02}$ when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the

O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

*Supplemental final analyses:* A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

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Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

## 11.5 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

*Construct and content*
The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items) [43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

*Descriptive analyses of baseline QOL scores*
Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean, standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

*Differences in FACT-TOI scores between patients receiving CT and CTB:* Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation

between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

*Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

*Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery.* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

## 11.6 Translational Research Statistical Considerations

*Overview*

The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

*Anticipated sample size for translational objectives*

The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately 198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1.

Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

*Training and validation set*

In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.

*Identifying biologic/molecular profiles*
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

*Reliability*
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which cannot be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

*Validation*
Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-

index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is known to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators, since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.7 The anticipated distribution of patients' race and ethnicity for the systemic therapy
portion of this trial is (all are female):

| | |
|---|---|
| White (not Hispanic) | 584 |
| Black (not Hispanic) | 39 |
| Hispanic | 14 |
| Asian | 17 |
| American Indian or Alaskan Native | 3 |
| Native Hawaiian or other Pacific Islander | 3 |

## 11.1 STATISTICAL CONSIDERATIONS - **Summary of Changes (Highlighted)**

### 11.2 Randomization**(10/01/12)**

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies: (All patients enrolled after August 28, 2011 will have their surgical cytoreductive treatment determined through randomization. These patients will select one of the following systemic treatments and declare their selection prior to enrollment onto the study) **(08/29/11)(12/19/11)**

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 GC: A standard regimen consisting of carboplatin (AUC 4) day 1 and gemcitabine (1000 mg/m$^2$) day 1 and 8 for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.13**CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment.

11.14 GCB: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until toxicity or progression necessitates discontinuing treatment early.

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.15 No cytoreductive surgery

11.16 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments (this sentence applies only to patients enrolled prior to Aug 29, 2011, thereafter patients select either CT, GC, GCB or CTB as their systemic treatment.). For those who consent to have cytoreductive surgery determined through randomization,

the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study **(08/29/11)**

11.3 Measures of Efficacy and safety

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

11.4 Treatment efficacy

*Overall type I error:* This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

*Expected median survival on the standard treatment:* Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

*Accrual target for evaluating the efficacy of systemic therapy*
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

*Statistical power for evaluating the efficacy of biologic therapy*: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: $H_{01}: D_{01} = l_{CTB} / l_{CT} \geq 1$ will be assessed, where $l$ is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their randomly assigned treatment. This comparison will not include those patients who were enrolled after August 28, 2011 and hence selected their systemic treatment. The

type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months). **(08/29/11)(12/19/11)**

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

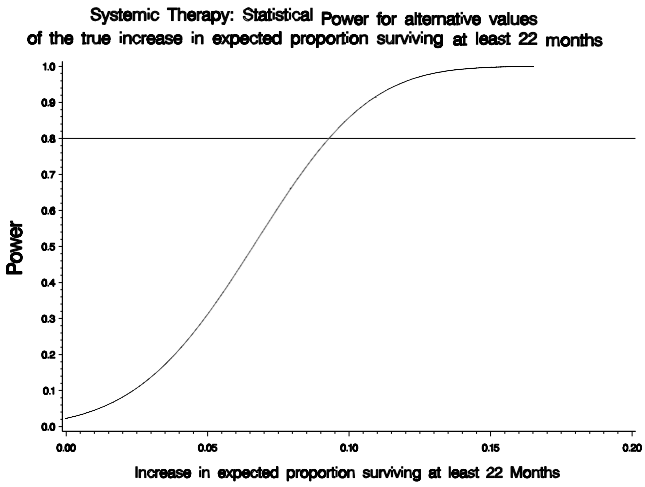


**Figure 1.**

*Statistical Power- evaluating the efficacy of surgical cytoreduction*: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival ($H_{02}$: $D_{02} = I_{surgery} / I_{No\ surgery} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their randomly assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment (CT vs CTB vs. CG vs CGB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12

months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses. **(08/29/11)(10/01/12)**

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, $H_{02}$, when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2. The anticipated total accrual for this component of the study is 360 patients.**(08/29/11)**

*An addendum to the statistical considerations following the amendment to extend recruitment to the surgical component of the study.* ***(12/19/2011)***

As of Nov-1-2011, there were 114 patients enrolled onto the surgical component of this study and 17 of these patients had died. The planned total number of patients to be enrolled onto the surgical component of this study is 360 patients. There were 35 patient enrolled during 2010, and 34 patients are projected to be enrolled during 2011. Therefore, assuming the future accrual is 35 patients per year, this study is expected to complete its targeted accrual in 7 years (Nov-2018). Patients enrolled after Aug-28-2011 will have their cytoreductive surgery determined by randomization. All of these patients will receive a standard carboplatin-paclitaxel regimen and permitted to choose whether to have bevacizumab supplement their treatment.

The data currently available from GOG-0213, indicates that the marginal hazard of death is approximately 0.021 $month^{-1}$. Assuming a constant hazard, the expected number of deaths when the accrual is completed among the 114 patients, who are already enrolled onto the surgical component of this study is 97.4. Assuming a similar death rate for all future patients, Simpson's rule (Schoenfeld, Biometrics 1983) can be used to estimate the number of patients among those who will be enrolled over the next 7 years and will have died when the accrual has been completed (130.1 deaths). Hence the expected total number deaths at the time when the target accrual is completed is 97.4+130.1 = 227.5. Likewise, the expected number of deaths reported 9 months after the targeted accrual is complete is 100.2+150.0=250.2, which is approximately the number required for the final analysis.

Therefore, the targeted date for completing the accrual to the surgical component of this study is Fall-2018. The required number of deaths required for the final analysis (250 deaths) is expected to occur nearly 1 year after the targeted accrual has been completed. In the event that the required number of deaths for the final analysis is observed before the targeted accrual is completed, then accrual will be stopped prior to attaining the targeted accrual. The planned analyses and the

power calculations provided above are unchanged by this revised recruitment plan.**(12/19/2011)**

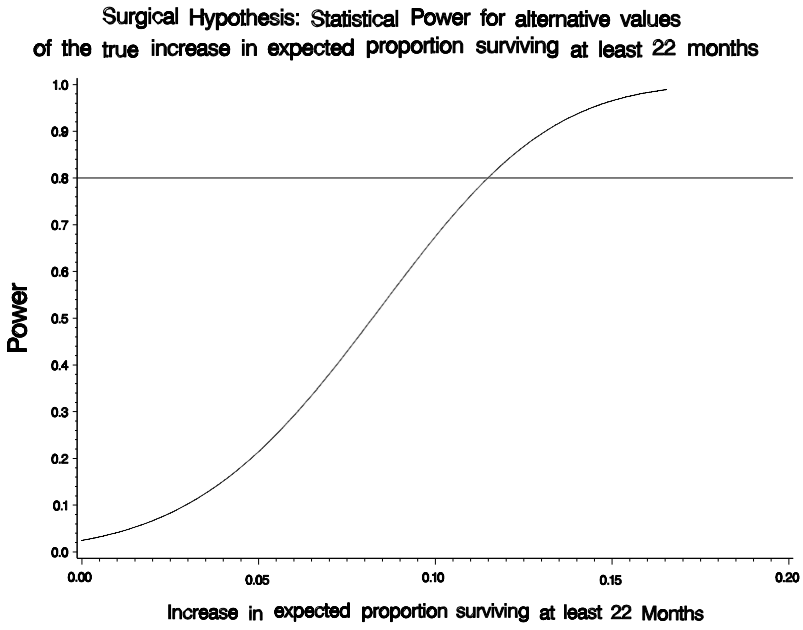


**Figure 2.**

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin with or without bevacizumab. It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.**(08/29/11)**

*Interim Analyses:* Interim analyses are planned when there are at least 110 deaths reported among all those patients randomly allocated (prior to August 29, 2011) to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and

July each year and the precise date of these meetings is set without confidential knowledge of the study results. **(10/01/12)**

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those randomly allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information time, $H_{01}$ will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis. **(08/29/11)**

$H_{02}$ will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of $H_{02}$ will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for $H_{01}$ (or $H_{02}$) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $D_{01} > 1.0$ (or $D_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%. The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

*Final analysis:* The study will be considered sufficiently mature to permit a final assessment of $H_{01}$ when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of $H_{02}$ when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the

O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

*Supplemental final analyses:* A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

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Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

## 11.5 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

*Construct and content*
The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items) [43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

*Descriptive analyses of baseline QOL scores*
Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean, standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

*Differences in FACT-TOI scores between patients receiving CT and CTB:* Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation

between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

*Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

*Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery.* This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

## 11.6 Translational Research Statistical Considerations

*Overview*

The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

*Anticipated sample size for translational objectives*

The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately 198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1.

Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

*Training and validation set*

In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.

*Identifying biologic/molecular profiles*
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

*Reliability*
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which cannot be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

*Validation*
Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-

index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is known to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators, since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.7 The anticipated distribution of patients' race and ethnicity for the systemic therapy
portion of this trial is (all are female):

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| White (not Hispanic) | 584 |
| Black (not Hispanic) | 39 |
| Hispanic | 14 |
| Asian | 17 |
| American Indian or Alaskan Native | 3 |
| Native Hawaiian or other Pacific Islander | 3 |

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: AUGUST 4, 2008

RE: PROTOCOL GOG-0213 – REVISION # 1

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version May 1, 2008***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**( ) Expedited review; however, site IRB requirements take precedence**
**(X) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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The following changes have been made and become effective: August 4, 2008

Title Page
- NCI version date has been updated. Includes: "Revision #1". Clarification to membership point distribution has been made. Patients who are surgical candidates are to be randomized to surgery or not. Six additional membership points are awarded for the randomization.
- Revised July 28, 2008, has been added to the footer. Title Page 2: Table with CTSU instructions has been deleted as Protocol GOG

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| | 0213 is not on the CTSU menu. Nurse Contact's address has been removed; e-mail, fax and phone were retained. |
| Table of Contents | - Appendix II: CTSU Logistical Information was deleted and the remaining appendices have been renumbered. Appendix VII: CTSU Specimen Consent Form has been deleted. References to appendices throughout the protocol document have been updated to reflect these changes. |
| Section 1.0 | - Fallopian tube carcinoma has been added throughout the section. |
| Section 2.10 | - In the last paragraph GOG 0213 patients are defined as "platinum-sensitive, recurrent epithelial-ovarian, peritoneal primary or Fallopian tube carcinoma" |
| Section 3.11 | - "Fallopian" was capitalized. |
| Section 3.13, 3.14 | - have been revised to expand eligibility to patients with non RECIST measurable recurrent disease. This group of patients had previously been entered onto another GOG protocol which recently closed. |
| Section 4.3 | - Drug information for bevacizumab has been updated as per the request of the PMB at CTEP |
| Section 4.32 | - The second paragraph regarding the investigational bevacizumab used in this trial not being the same as commercial Avastin has been deleted, per an Amendment Request from CTEP, dated January 16, 2008 |
| Section 4.35 | - The CAEPR has been updated with the June 19, 2007 version. |
| Sections 4.38-4.40 | - Agent Ordering and Accountability have been replaced per the instructions of the PMB at CTEP. |
| Section 5.233 | - Now states that the bevacizumab will be administered as a 'short' IV infusion following paclitaxel. |
| Section 5.242 | - The maximum number of cycles has been increased from 6 to 8 for patients with stable or partial regression of their disease as maximum documented response. |

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| Section 5.252 | - The maximum number of cycles has been increased from 6 to 8 for patients with stable or partial regression of their disease as maximum documented response. |
| Section 6.1612 | - 'Carboplatin' has been deleted, dose is not recalculated due to weight loss. |
| Section 7.1 | - The following has been added: "The stained pathology slides required for central review by the GOG Pathology Committee to confirm eligibility are defined in the footnote in Section 10.2"<br>- In the table after "Radiographic Tumor Measurement" "See footnote 11 c) and d)" has been added for clarification. C) and d) have been **bolded**. |
| Section 7.21 | - Reference to Section 10.3 has been corrected to 10.2.<br>-Quick Scan Summary of the Specimen Requirements has been updated. Footnote 4 includes Fallopian tube. |
| Section 7.2111 | - Now states 'Primary" or Metastatic Tissue for "Translational" Research. |
| Section 7.2112 | - Has been updated to reflect changes made to Section 7.21 above. |
| Section 7.234 | - Now states that all proteomic studies will be performed by a Group approved by the GOG Committee for Experimental Medicine |
| Section 7.31 | - Now states that the requests for the FACT-O in Spanish or French should be made to the GOG Statistical and Data Center not Drs Wenzel or Basen-Enquist. |
| Section 10.141 | - "In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 215-854-0716. A 24-hour notification is to be made to the GOG Regulatory Department by telephone at 215-854-0770, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site." has been added in the event that an institution cannot file an event electronically. |

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| Section 10.2 | - E-mail address for the Tissue bank has been updated. Changes outlined in 7.21 have been made in this section as well. "Complete" has been deleted. This study will be monitored by the Abbreviated CDUS. |
| Appendix II | - Has been deleted. |
| Appendix III | - Has been renumbered Appendix II |
| Appendix IV | - Has been renumbered Appendix III |
| Appendix V | - Has been renumbered Appendix IV and has been updated with the changes made in Section 7.21 |
| Appendix VI | - Has been deleted |
| Informed Consent | - NCI version date has been updated.<br>- Under "Why is This Study Being Done?" in the second paragraph language about the differences between commercially available Avastin has been deleted per the request of PMB at CTEP.<br>- A seventh paragraph has been added: "Another purpose of this study is to test samples of your blood, some of your tumor if left over from a previous surgery and some of your tumor and normal tissue if left over from surgery performed as part of this study. The purpose of this research is to determine if this testing can be used in the future to determine which patients may respond to treatment or have a good prognosis.<br>- Under "What will happen if I take part in this research study? After the explanation of the two possible chemotherapy combinations the following paragraph has been added: "If you and your doctor determine that you are a surgical candidate you will be asked to give permission to provide some of your specimens (2 tubes of blood), samples of your tumor if left over from a previous surgery, and some of your tumor and normal tissue if left over from surgery performed as part of this study, for laboratory testing that is not part of regular cancer care and is being done only because you are in this study. You can still participate in this study if you do not give permission for your specimens to be collected and used for this optional research. For more information on this optional research please see the last |

three sections of this document. One section provides general information about the collection and use of specimens for research. Another section describes specific information about the use of specimens for this research study. The last section focuses on issues regarding future research."

- Under "What about Confidentiality?" in the last sentence "This will include the Data Safety and Monitoring Board which reviews adverse event reports to assure patient safety" has been added as a reviewer of patient records.

- The fifth paragraph has been added: "When the research results are published or discussed in conferences, no information will be included that reveals your identity. In a few rare situations, federal or state law requires disclosure of personal information. Examples of these instances are reporting of child abuse or abuse of an elderly person."

-Under "What are the Costs?" The following statement has been added: "You will be responsible for paying any deductibles, coinsurance and copayments as required under the terms of your insurance plan(s)" The second paragraph has been revised to state that if patient should need bevacizumab for much longer than is usual, NCI free supply of the agent could run out. If this were to happen patient's doctor would discuss with her how to obtain additional drug from manufacturer and patient may be asked to pay for it.

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

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**TO:** ALL GOG MEMBER INSTITUTIONS
ALL PRINCIPAL INVESTIGATORS/ NURSES/DATA MANAGERS

**FROM:** GOG REGULATORY AFFAIRS DEPARTMENT

**DATE:** DECEMBER 15, 2008

**SUBJECT:** UPDATED INVESTIGATORS BROCHURE FOR BEVACIZUMAB

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The Pharmaceutical Management Branch (PMB) has updated the Investigator's Brochure for Bevacivumab. If your investigators wish to obtain a copy of this IB, please forward your request to: IBCOORDINATOR@MAIL.NIH.GOV

Please note that all investigators receiving this agent from the PMB for an NCI-sponsored clinical trial have already received a copy of this IB directly from the PMB.

This agent is currently being used on the following GOG studies:

**GOG-0213**
**GOG-0218**
**GOG-0229G**
**GOG-0251**
**GOG-9917**

If you have any questions, or comments, please contact the Pharmaceutical Management Branch at (301)-496-5725 or at ibcoordinator@mail.nih.gov .

sg

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: MAY 18, 2009

RE: PROTOCOL GOG-0213 – REVISION # 2

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version March 6, 2008***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

( ) **No review required**
(X) **Expedited review; however, site IRB requirements take precedence**
( ) **Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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The following changes have been made and become effective May 18, 2009.

Title Page -NCI version date has been updated. "Whole blood draw has been added; 0.5 point will be awarded for submission.

Schema -"The banking of whole blood for future research will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0213." has been added.

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| Table of Contents | - Appendix II FACT-O has been deleted and the remaining appendices have been re-numbered. |
| Section 1.53 | - "To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events." has been added. |
| Section 2.9 | - References to Appendix II have been deleted as the appendix was removed from the T.O.C. |
| Section 2.11 | - A new section, "Rationale for Whole Blood Banking for Future Research," has been added. |
| Section 2.12 | - A new section, "Single Nucleotide Polymorphisms (SNPs) and SNP Profiling," has been added. Remaining sections have been renumbered. |
| Section 3.133 | - Now states that: Patients receiving maintenance biologic "or hormonal therapy" are eligible. |
| Section 3.134 | - "Patients who have undergone reassessment laparotomy or laparoscopy following primary therapy are eligible as long as they demonstrated a pathologic complete response based on the surgical assessment (i.e. all obtained specimens were histologically negative for disease)" was deleted. |
| New Section 3.134 | -A new Section has been added: "Patients on GOG-0198 or patients receiving hormonal therapy for biochemical or non-measurable recurrent disease are ELIGIBLE provided their recurrence is documented more than 6 months following the completion of primary cytotoxic chemotherapy. A minimum of 4 weeks must have expired since their last exposure to hormonal therapy." |
| Section 3.141 | - At the end of the section: "Note: Patients with biochemical recurrence, by definition, are not eligible for surgical randomization and should be considered for the chemotherapy randomization alone." has been added. |
| Section 3.143 | - At the end of the section: "Note: Patients with non-measurable, clinically-evident disease, by definition, are not eligible for |

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| | surgical randomization and should be considered for the chemotherapy randomization alone." has been added |
| Section 3.26 | -"other than ovarian, fallopian tube and primary peritoneal" have been added. |
| Section 4.0 | - Shipment schedule has been deleted. Institutions are responsible for ordering drug themselves. GOG does not order drug. |
| Section 4.37 | - typographical errors have been corrected: "leukoencepalopathy" is now "leukoencephalopathy". "Bevaciumab" is now "bevacizumab" "neutorpenia" is now "neutropenia" |
| Section 4.6 | -"Pathology Requirements" have been added. |
| Section 5.22 | - Reference to Appendix III has been corrected to II. |
| Section 5.231 | - Rows for Regimens III and IV have been added to the table. A column has been added for Surgery. |
| Section 5.237 | -"Dosing of Paclitaxel" section has been added and is cross-referenced with Section 6.1612 for dose modifications based upon weight change of 10% or more. |
| Section 5.238 | -" Dosing of bevacizumab" was moved from Section 5.255. It now states: "**For patients randomized to the chemotherapy arm**" the weight at screening… recalculated." Supportive care guidelines have been added. |
| Section 5.24 | -"Arm I" has been changed to "Paclitaxel and Carboplatin (Arm I and Arm III):" |
| Section 5.242 | -The first reference to Section 8.14 has been changed to 8.15 |
| Section 5.25 | -"Arm II" has been changed to: Carboplatin, Paclitaxel and Bevacizumab (Arm II and Arm IV) |
| Section 5.3 | - References to Appendix numbers have been corrected. |
| Section 6.142 | -**Thrombosis:** Tables B-1 and B-2 have been updated to include all Arms on this study. |

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| Section 6.164 | - **Proteinuria:** UPC ratio "less than 3.5" is now "less than or equal to 3.5". "*Please note chemotherapy may be administered if bevacizumab is held for Grade 3 proteinuria." has been added. |
| Section 6.1613 | - Clarification has been made regarding resumption of treatment with bevacizumab in patients with documented benefit. |
| Section 7.1 | - See Section 7.2…has been added to direct institutions to pathology requirements.<br>- Clarification has been made to maintenance/surveillance phase<br>- Urine pregnancy test has been added for women of childbearing potential. Serum CA-125 is to be performed every 3 months on patients in maintenance/ surveillance phase.<br>- Footnotes 3, 10, 11c,d ,12, and 13: have been updated. |
| Section 7.2 | - New section has been added to reflect Pathology requirements for Central review. |
| Section 7.3 | - Previous Section 7.2 has been renumbered and title has been changed to "Translational Research." |
| Section 7.31 | -"The collection of a whole blood for DNA extraction and single nucleotide polymorphism (SNP) analysis will apply to all women on GOG-0213 who provide consent regardless of randomization and treatment including those already enrolled on protocol. Women who are already enrolled on GOG-0213 will need to be re-consented." has been added as a second paragraph.<br>- "Quick Scan Summary of Specimen Requirements : Collection Time points and Requirements" has been modified to state "for patients who provide consent"<br>- Required Specimens for Whole Blood banking information has been added.<br>- References to Appendix numbers have been corrected.<br>- Footnotes have been updated. Footnotes 6 and 7 have been added. Remaining subsections have been renumbered. |
| Section 7.33 | - Laboratory Testing has been updated relative to the Whole Blood draw. The address of Dr Birrer's lab has been updated to reflect his move to MGH. |
| Section 7.335 | - Has been added relative to the Whole Blood draw. |

Section 7.34 - "Future Research See Section XII in Appendix III for important details regarding the banking and distribution of the residual tumor, tissue, serum or plasma specimens still remaining after completion of GOG-0213 and any whole blood collected from women on GOG-0213 for future research." has been added.

Section 7.4 - Previously Section 7.3 has been renumbered.

Section 8.14 - Progression: the seventh bullet "Progression based on serum CA125" has been deleted.

Section 10.2 - "Archival Formalin-Fixed and Paraffin Embedded" includes abbreviation "FFPE". Editorial changes were made within the tabled. Instructions for submission through SEDES have been clarified.
- Form SP-WB01-213 has been included.
- Footnotes *f*,†, ‡, and ‡‡ have been added.

Informed Consent - The NCI version date has been updated.
Under "**WHY IS THIS STUDY BEING DONE?"** in the last paragraph the last sentence "have side effects" has been added.

- Under "**WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?"** In the last **two** paragraphs language has been added to explain that an additional two teaspoons of blood are requested for future research. Information directing patient to other sections of the consent has been moved to this paragraph.

- "tubes of blood (2 teaspoons)" has been changed to "provide some of your specimens (4 teaspoons)" to include the whole blood draw that has been added in this amendment.

- Under "**WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?**" "may be life threatening" has been changed to "may result in death"

- Under **WHAT ABOUT CONFIDENTIALITY?** In the first paragraph "may' has been inserted after "GOG procedures." In the fifth paragraph the following has been removed: " In a few rare situation, federal or state law requires disclosure of personal information. Examples of these instances are reporting of child abuse or abuse of an elderly person."

- Under **WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?** This section has been updated

with standard template language.

- Under "**GENERAL INFORMATION ABOU THE COLLECTION AND USE OF SPECIMENS FOR RESEARCH**" Language has been added to the first paragraph relative to the Whole Blood draw that has been included for all patients. The final sentence now includes: "and why some people have or don't have side effects to cancer therapies,"
- In the last paragraph "your specimens will be used for research purposes only until they are used up" has been added.

- Under "**SPECIFIC INFORMATION FOR THIS RESEARCH STUDY"** Language has been added to reflect the additional collection of blood from all patients entered on study, not just those undergoing secondary cytoreduction.

- Under **SPECIFIC INFORMATION FOR FUTURE RESEARCH :** "Either natural changes or" has been added to the first sentence in the second paragraph,

- Under "**MAKING YOUR CHOICES FOR THIS RESEARCH STUDY,** in the third question "drawn to prepare serum and plasma for" has been changed to "collected for."

Appendix II - Has been removed and the remaining appendices have been renumbered. All references throughout the protocol have been corrected.

Appendix III - Specimen Procedures for GOG-0213 has been updated to include instructions for preparation of whole blood (notably addition of Section VII) and the distribution of specimens for future research (revision and expansion of Section VI Section XI). In addition, references to protocol sections were updated, as was location of Dr. Birrer's lab

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

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*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: JUNE 15, 2009

RE: PROTOCOL GOG-0213 – REVISION # 2

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version March 6, 2009***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

---

The following changes have been made and become effective **June 22, 2009.**

| | |
|---|---|
| Title Page | -NCI version date has been updated. "Whole blood draw has been added; 0.5 point will be awarded for submission. |
| Schema | - The paragraph following the flowchart has been completely updated. |
| Table of Contents | - Appendix II FACT-O has been deleted and the remaining appendices have been re-numbered. |

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| Section 1.53 | - "To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events." has been added. |
| Section 2.9 | - References to Appendix II have been deleted as the appendix was removed from the T.O.C. |
| Section 2.11 | - A new section, "Rationale for Banking DNA from Whole Blood for Research," has been added. |
| Section 2.12 | - A new section, "Single Nucleotide Polymorphisms (SNPs) and SNP Profiling," has been added. Remaining sections have been renumbered. |
| Section 3.133 | - Now states that: Patients receiving maintenance biologic "or hormonal therapy" are eligible. |
| Section 3.134 | - "Patients who have undergone reassessment laparotomy or laparoscopy following primary therapy are eligible as long as they demonstrated a pathologic complete response based on the surgical assessment (i.e. all obtained specimens were histologically negative for disease)" was deleted. |
| New Section 3.134 | -A new Section has been added: "Patients on GOG-0198 or patients receiving hormonal therapy for biochemical or non-measurable recurrent disease are ELIGIBLE provided their recurrence is documented more than 6 months following the completion of primary cytotoxic chemotherapy. A minimum of 4 weeks must have expired since their last exposure to hormonal therapy." |
| Section 3.141 | - At the end of the section: "Note: Patients with biochemical recurrence, by definition, are not eligible for surgical randomization and should be considered for the chemotherapy randomization alone." has been added. |
| Section 3.143 | - At the end of the section: "Note: Patients with non-measurable, clinically-evident disease, by definition, are not eligible for surgical randomization and should be considered for the chemotherapy randomization alone." has been added |

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| Section 3.26 | -"other than ovarian, fallopian tube and primary peritoneal" have been added. |
| Section 4.37 | - typographical errors have been corrected: "leukoencepalopathy" is now "leukoencephalopathy". "Bevaciumab" is now "bevacizumab" "neutorpenia" is now "neutropenia" |
| Section 4.40 | - Shipment schedule has been deleted. Institutions are responsible for ordering drug themselves. GOG does not order drug. |
| Section 4.4 | - This entire section is now Docetaxel information, in the prior version it was a combination of 4.4, 4.5 and 4.6 and this has now been corrected. |
| Section 4.5 | -"Pathology Requirements" have been added. |
| Section 5.22 | - Reference to Appendix III has been corrected to II. |
| Section 5.231 | - Rows for Regimens III and IV have been added to the table. A column has been added for Surgery. |
| Section 5.237 | -"Dosing of Paclitaxel" section has been added and is cross-referenced with Section 6.1612 for dose modifications based upon weight change of 10% or more. |
| Section 5.238 | -"Dosing of bevacizumab" was moved from Section 5.255. It now states: "**For patients randomized to the chemotherapy arm**" the weight at screening… recalculated." Supportive care guidelines have been added. |
| Section 5.24 | -"Arm I" has been changed to "Paclitaxel and Carboplatin (Arm I and Arm III):" |
| Section 5.242 | -The first reference to Section 8.14 has been changed to 8.15 |
| Section 5.25 | -"Arm II" has been changed to: Carboplatin, Paclitaxel and Bevacizumab (Arm II and Arm IV) |
| Section 5.3 | - References to Appendix numbers have been corrected. Also Section 7.2 is now Section 7.3. |
| Section 6.143 | -**Thrombosis:** Tables B-1 and B-2 have been updated to include all Arms on this study. |

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|---|---|
| Section 6.164 | - **Proteinuria:** UPC ratio "less than 3.5" is now "less than or equal to 3.5". "*Please note chemotherapy may be administered if bevacizumab is held for Grade 3 proteinuria." has been added. |
| Section 6.1613 | - Clarification has been made regarding resumption of treatment with bevacizumab in patients with documented benefit. |
| Section 7.1 | - See Section 7.2…has been added to direct institutions to pathology requirements.<br>- Clarification has been made to maintenance/surveillance phase, added "(Patients on Arm II and IV only)".<br>- Urine pregnancy test has been added for women of childbearing potential. Serum CA-125 is to be performed every 3 months on patients in maintenance/ surveillance phase.<br>- Footnotes 3, 10, 11c, 11d, 12, and 13: have been updated. |
| Section 7.2 | - New section has been added to reflect Pathology requirements for Central review. |
| Section 7.3 | - Previous Section 7.2 has been renumbered and title has been changed to "Translational Research." |
| Section 7.31 | -"The collection of a whole blood for DNA extraction and single nucleotide polymorphism (SNP) analysis will apply to all women on GOG-0213 who provide consent regardless of randomization and treatment including those already enrolled on protocol. Women who are already enrolled on GOG-0213 will need to be re-consented." has been added as a second paragraph.<br>- Reference to Appendix IV has been changed to Appendix III throughout this section.<br>- The "Quick Scan Summary of Specimen Requirements" table and the proceeding footnotes have been updated completely to accurately reflect the translational research collection for this study<br>- Remaining subsections have been renumbered.<br>- In the previous version there was a section titled "Tissue Specimens", this has been deleted. |
| Section 7.33 | - Laboratory Testing has been updated relative to the Whole Blood draw. The address of Dr Birrer's lab has been updated to reflect his move to MGH. |

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|---|---|
| Section 7.332-7.334 | - Dr. Birrer's lab location has been updated from NCI to MGH and reference to analysis being done by investigators approved by CEM based on available funding and expertise has been added. |
| Section 7.335 | - New section, "SNP Analysis". |
| Section 7.34 | - "Future Research See Section XII in Appendix III for important details regarding the banking and distribution of the residual tumor, tissue, serum or plasma specimens still remaining after completion of GOG-0213 and any whole blood collected from women on GOG-0213 for future research." has been added. |
| Section 7.4 | - This is now the Quality of Life Section, previously this was the Central Pathology Review section. |
| Section 8.14 | - Progression: the seventh bullet "Progression based on serum CA125" has been deleted. |
| Section 10.2 | - The names of all the forms have been added.<br>- Form OSR has been added<br>- Form BDR has been removed<br>- "Archival Formalin-Fixed and Paraffin Embedded" includes abbreviation "FFPE".<br>- Instructions for submission through SEDES have been clarified.<br>- Form BMR has been added<br>- Form SP-WB01-213 has been included.<br>- FACT-O, "Scantron Form" has been added.<br>- Footnotes *f*,†, ‡, and ‡‡ have been added. The following footnotes have been updated: *, **, ±, $^{\nabla}$. The following footnote was deleted "$^{\nabla\nabla}$". |
| Informed Consent | - The NCI version date has been updated.<br>Under **"WHY IS THIS STUDY BEING DONE?"** in the last paragraph the last sentence "have side effects" has been added.<br><br>- Under **"WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?"** In the last paragraph language has been added to explain that an additional two teaspoons of blood are requested for future research. Information directing patient to other sections of the consent has been moved to this paragraph.<br><br>- Under **"WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?"** "may be life threatening" has been changed to "may result in death" |

- Under **WHAT ABOUT CONFIDENTIALITY?** In the first paragraph "may' has been inserted after "GOG procedures." In the fifth paragraph the following has been removed: "In a few rare situations, federal or state law requires disclosure of personal information. Examples of these instances are reporting of child abuse or abuse of an elderly person."

- Under **WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?** This section has been updated with standard template language.

- Under "**GENERAL INFORMATION ABOU THE COLLECTION AND USE OF SPECIMENS FOR RESEARCH**" Language has been added to the first paragraph relative to the Whole Blood draw that has been included for all patients. The final sentence now includes: "and why some people have or don't have side effects to cancer therapies,"
- In the last paragraph "your specimens will be used for research purposes only until they are used up" has been added.

- Under "**SPECIFIC INFORMATION FOR THIS RESEARCH STUDY"** Language has been added to reflect the additional collection of blood from all patients entered on study, not just those undergoing secondary cytoreduction. The section identified as "Specimen Requirements (only for the specific subset of patients identified above)" has been deleted as this is no longer applicable.

- The "**WHAT WILL HAPPEN TO YOUR SPECIMENS IF YOU AGREE**?" has been completed rewritten.

- Under "**MAKING YOUR CHOICES FOR THIS RESEARCH STUDY,** in the third question "drawn to prepare serum and plasma for" has been changed to "collected for."
- Under **SPECIFIC INFORMATION FOR FUTURE RESEARCH :** "Either natural changes or" has been added to the first sentence in the second paragraph.

Appendix II - Has been removed and the remaining appendices have been renumbered. All references throughout the protocol have been corrected.

Appendix III - Specimen Procedures for GOG-0213 has been updated to include

instructions for preparation of whole blood (notably addition of Section VII) and the distribution of specimens for future research (revision and expansion of Section VI Section XI). In addition, references to protocol sections were updated, as was location of Dr. Birrer's lab

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: MARCH 15, 2010

RE: PROTOCOL GOG-0213 – Amendment request, Revision #3

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, FALLOPIAN TUBE AND PERITONEAL PRIMARY CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version February 23, 2010***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**
**IRB Review Recommendation:**

**(X) No review required**
**( ) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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The following changes have been made:

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|---|---|
| Title Pages | - NCI version date has been updated.<br>"Includes Revisions 1-3" has been added. |
| Section 3.153 | - "Creatinine ≤ 1.5 mg/dL (133 < mol/l) or" has been deleted.<br>"Estimated" has been added. |

| | |
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| Section 3.26 | - "Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than five years prior to registration, and that the patient remains free of recurrent or metastatic disease." Has been deleted. |
| Section 3.386 | -"(less than 24hrs)" has been deleted. "< 24 hrs in duration, that are…" was added after "episodes of ischemia". |
| Section 3.392 | - Has been clarified to reflect that patients must be 28 days out from surgery other than cytoreduction to begin protocol treatment. Patients who undergo an uncomplicated port placement must wait a minimum of 7 days to begin protocol treatment. |
| Section 5.22 | - "A discussion with the study chair is required if study treatment is not initiated within 6 weeks of surgery." Was added. |
| Section 5.231 | -Agents are now listed in the order they are administered. |
| Section 5.233 | -Agents are now listed in the order they are administered. |
| Section 5.236-8 | -Agents are now listed in the order they are administered. |
| Section 5.25 | -Agents are now listed in the order they are administered. |
| Section 6.1 | - The following was added after the first paragraph: "If a dose reduction is indicated, recalculate chemotherapy dosages using the baseline weight and serum creatinine." |
| Section 6.141 | - **Hemorrhage:** Clarification has been made that bevacizumab alone is to be held. Carboplatin and paclitaxel will be continued. |
| Section 6.142 | -**Thrombosis:** Venous Thrombosis: Clarification has been made that all therapy will be held. |
| Section 6.143 | -**Coagulopathy:** Clarification has been made that all therapy will be held. |
| Table B-1 | - Agents are now listed in the order they are administered. |
| Section 6.151 | -"Cycle" is now "chemotherapy cycle" "No subsequent cycle of maintenance bevacizumab shall begin until the ANC is ≥ 1000/mcl and platelets are ≥ 75,000/mcl." Was added to the end of the section. |

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| Section 6.153 | - "less than" is now "≤" "Patients who have a delay of > 2 weeks will have a one level dose reduction and the addition of myeloid growth factors in all subsequent cycles." Was added to the end of the section. |
| Section 6.161 | - **Neurologic toxicity** Has been clarified to reflect that all agents will be held. "If peripheral neuropathy fails to recover to Grade ≤ 2 by a maximum delay of three weeks from time therapy is due, then the patient is removed from study." Was deleted from the end of the section. |
| Section 6.168 | - **Hypertension**: Second bullet has been clarified to reflect that all agents will be held. |
| Section 6.1613 | -" unless the patient meets the criteria below." Was added to the end of the section. |
| Section 7.1 | - CBC/Diff/platelets are to be done prior to every course during the Maintenance phase, not prior to every other course. This has been changed. The very last column in the table: "Q 3 Months x 8 then q 6 months" is for all patients, not only those on Arms II and IV<br>-Footnote 11e was added and former 11e is now 11f. |
| Section 7.31 | -Footnote 3 "FP01" has been corrected to "FT01" |
| Section 10.2 | - # has been added to Forms D2M, T and D2R.<br>Comment column of table "FP01" has been corrected to "FT01" |
| Informed Consent | - The NCI version date has been updated |

There were no changes made to the appendices

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

**Philip J. DiSaia, M.D.**
*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: AUGUST 23, 2010

RE: PROTOCOL GOG-0213 – Revision #4

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, FALLOPIAN TUBE AND PERITONEAL PRIMARY CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version August 9, 2010***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

**NOTE: Although there are changes to the risk language there were not changes to the risk-benefit ratio hence the recommendation for expedited review.**
Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

---

This amendment is being submitted in response to an RA from Dr. Helen Chen (Helen.chen@nih.gov; 301-496-1196). The following changes have been made:

Section 4.36 - The CAEPR for Bevacizumab has been updated. It is now Version 2.1, May 4, 2010. This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious.

Informed Consent
- The NCI version date has been updated
- Under "What Side Effects or Risks Can I Expect from being in the Study?"
  - The risks and side effects of bevacizumab have been updated with the inclusion of CAEPR version 2.1:
    - Added New Risks:
      - Less Likely: Abnormal Changes in the growth plate that may affect the growth of long bones in very young children. This side effects appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug; Blood in the urine.
      - Rare but Serious: Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure.
    - Changed to Less Likely from Reported but Undetermined:
      - Infection (collection of pus) around the rectum; fainting.

The following additional changes have been made:

Title Pages
- NCI version date has been updated. "Includes Revisions 1-4" has been added.

Section 3.153
- "Estimated creatinine clearance ≥ 60 ml/min" has been replaced with: Creatinine (non-IDMS) ≤ 1.5 x institutional upper limit normal (ULN), CTCAE Grade 1".

Section 5.238
- "non- IDMS" was inserted before "serum creatinine" and "creatinine" throughout this section.
- Second bullet: reference to section "6.153" has been corrected to "6.163"

Section 6.161
- Has been clarified to state that patients with persistent Grade 2 neurotoxicity will have docetaxel substituted for paclitaxel. Patients with persistent Grade 3-4 neurotoxicity should be removed from study.

Section 8.14
- Seventh bullet and three ° sub-sections have been added:
  - Progression based on serum CA-125:

- Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

- or -

- Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

- or -

- Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression.

- In the last paragraph of the section that begins Progression (non-measurable disease) the last sentence was changed **from** "Date of progression will be the date of the first confirmatory CA-125 level." **To** "If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression."

Section 8.15 - After the last bullet indentation the following language was added: "When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression."

There were no changes made to the appendices

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

**FOR YOUR CONVENIENCE, AND TO FACILITATE LOCAL IRB REVIEW, A COPY OF THE INFORMED CONSENT WITH ALL CHANGES TRACKED IS BEING POSTED INADDITION TO THE CLEAN VERSION.**

**Philip J. DiSaia, M.D.**
*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: AUGUST 9, 2011

RE: PROTOCOL GOG-0213 – Update 8/9/11

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, FALLOPIAN TUBE AND PERITONEAL PRIMARY CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version December 2, 2010***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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The following changes have been made and become effective August 9, 2011:

Title Pages
- Update date has been added.
- PER CAPITA points have been reduced from 30 to 14.

The trial has met and is exceeding the accrual goal for the primary study objective. An amendment request has been submitted to CTEP to keep the

trial open until the accrual goal for the surgical component has been met. If the amendment is approved it will be broadcast to the Group immediately. In the meantime we have reduced the payment points all new patient entries.
It is unknown if there will be adequate funding to increase the points but we will know that when and if we broadcast the amendment. If the amendment is not approved the trial will be closed.

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: SEPTEMBER 26, 2011

RE: PROTOCOL GOG-0213, REVISION # 7

**Protocol Title:** A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version 09/09/11***

Study Chair: Robert L. Coleman , M.D., (713) 745-3357; email: **rcoleman@mdanderson.org**

**IRB Review Recommendation:**
**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the informed consent.**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

---

The following changes have been made in response to CTEP's mandate to convert all CTCAE v3.0 studies over to CTCAE v4.0 by a certain date. The changes are to inform the site that all reports through AdEERS should be made using the CTCAE v4.0 criteria, however all toxicities reported on the T form should still be submitted using CTCAE v3.0.

These changes become effective September 26, 2011:

| | |
|---|---|
| Title Pages | NCI Version date has been updated.<br>Includes Revisions 1-7.<br>Revised has been added to the footer. |
| Section 10.11 | Deleted 2nd paragraph which referred to CTCAE Version 3.0. |

| | |
|---|---|
| Section 10.13 | Added two paragraphs under "Reporting Requirements for Adverse Events that occur within 30 Days of the Study Procedure"<br>• 1st paragraph specifies CTCAE v. 3.0 utilized from study activation until September 30, 2011.<br>• 2nd paragraph states CTCAE v.4.0 will be utilized *beginning October 1, 2011* and provides website locations. |
| Section 10.141 | -Sub-section has been updated with most recent reporting requirements.<br><br>-A paragraph has been added to outline the conversion to CTCAE v4 and the reporting procedures to be used starting October 1, 2011. |
| Section 10.21 | - Sub-section has been updated with most recent reporting requirements.<br>- Deleted 2nd paragraph which referred to CTCAE Version 3.0. |
| Section 10.23 | - Added two paragraphs under "Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent on Phase 2 and 3 trials"<br>• 1st paragraph specifies CTCAE v. 3.0 utilized from study activation until September 30, 2011.<br>• 2nd paragraph states CTCAE v.4.0 will be utilized *beginning October 1, 2011* and provides website locations. |
| Section 10.241 | -Sub-section has been updated with most recent reporting requirements.<br><br>-A paragraph has been added to outline the conversion to CTCAE v4 and the reporting procedures to be used starting October 1, 2011. |
| Section 10.31 | - Added two paragraphs under "Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Commercial Agent on Phase 2 and 3 trials"<br>• 1st paragraph specifies CTCAE v. 3.0 utilized from study activation until September 30, 2011.<br>• 2nd paragraph states CTCAE v.4.0 will be utilized *beginning October 1, 2011* and provides website locations. |
| Section 10.4 | -Added below footnotes, "This study utilizes the Common Terminology Criteria for Adverse Events version 3.0..." |
| Informed Consent | NCI version date has been updated. |

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

**Philip J. DiSaia, M.D.**
*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: AUGUST 29, 2011

RE: PROTOCOL GOG-0213 – Revision #6

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, FALLOPIAN TUBE AND PERITONEAL PRIMARY CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version 07/27/11***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**( ) Expedited review; however, site IRB requirements take precedence**
**(X) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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This amendment was submitted and approved due to the fact that the accrual goal had been met for the primary objective but the surgical component has not been adequately accrued. As stated in Section 11.3, paragraph nine:
"*In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical*

*cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue."*

The following changes have been made in support of this amendment and become effective August 29, 2011:

| | |
|---|---|
| Title Pages | - NCI version date has been updated.<br>- Per capita points have been reduced from 30 to 14<br>- Includes revisions 1-6<br>-Study Co-chair Scott Eisenkop has been replaced with Nicola Spirtos.<br>- Nurse Contact Jacalyn Gano has been replaced by Maria Jung<br>- Revised has been added to the footer. |
| Schema | - Has been modified to reflect that the randomizations to chemotherapy regimens will be eliminated after 8-7-11 and only the surgical randomization remains. |
| Appendix III | - Information regarding shipping to the GOG Tissue Bank has been updated. |
| Section 3.10 | - Has been added: "Patients enrolled after August 7, 2011 must be candidates for cytoreductive surgery and consent to have their surgical treatment determined by randomization." |
| Section 3.134 | -Has been deleted as those patients are no longer eligible because they don't have measurable disease. |
| Section 3.14 | - Now states: "Patients must have-clinically evident, recurrent disease for the purpose of this study. |
| Section 3.141 | -Was deleted as it referred to patients with only biochemical determined disease. |
| Section 3.143 | -Was deleted as it referred to patients with non-measurable disease. |
| Section 3.16 | - Includes statement: "This eligibility criterion does not apply to patients enrolled after August 7, 2011" |
| Section 3.235 | - Has been added: "Patients whom have already undergone secondary cytoreduction for recurrent disease are excluded" |
| Section 5.21 | -Second paragraph includes disclaimer: "The following two sentences do not apply to patients enrolled onto the study after August 7, 2011)" |

| | |
|---|---|
| Section 5.23 | - Includes statement that the chemotherapy randomization was conducted between Dec 6, 2007 and August 7, 2011. |
| Section 5.233 | - Typographical error was corrected: "...docetaxel will be administered...dose of 175 mg/ $m^2$ ..." |
| Section 5.237 | - Numbering of the subsection has been corrected: 5.2381 is now 5.2371. |
| Section 6.167 | -References 74, 75 have been corrected to "45, 46" |
| Section 7.1 | - Footnote 11(f) "every three months is now "every three months for two years and then every six months" Reference to Section 8.3 has been corrected to 8.14 and 8.15. |
| Section 7.31 | -Footnote 6 below the table has been revised to direct institutions to the new Kit Management application for submission to the GOG Tissue Bank. |
| Section 10.1 | -New section "ADVERSE EVENT REPORTING FOR A TRIAL EVALUATING A SURGICAL PROCEDURE" was added. |
| Section 10.2 | -Was renumbered from 10.1, title has been changed to include: "TO USE FOR PATIENTS WHO SELECT BEVACIZUMAB AFTER AUGUST 7, 2011" Subsections have been renumbered.<br><br>Section 10.241- "Please consult these guidelines for secondary malignancy (including AML, MDS) reporting requirements." was deleted. Second paragraph has been added: "AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-possibly related to cancer treatment (specify)". The fourth paragraph has also been revised to read: "In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted. |
| Section 10.3 | -"Adverse event reporting for a commercial agent (to be used for patients not taking bevacizumab after August 7, 2011)" has been added. |

| | |
|---|---|
| Section 10.4 | -Was renumbered from 10.3 to 10.4. |
| Section 11.0 | -Has been revised through-out to reflect the changes that would be effective once the trial is open to surgical candidates alone. The anticipated total accrual for this component of the trial is 360 patients. |
| Informed Consent | - The NCI version date has been updated<br>-Under: "WHY IS THIS STUDY BEING DONE?" In the second paragraph, lung and breast cancer have been added to the list of uses approved by the FDA for bevacizumab. A fourth paragraph has been added which explains that patients may choose whether or not to receive bevacizumab. Language relative to the chemotherapy randomization has been deleted to be consistent with changes to protocol.<br>- Under: "HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?" "660 has been changed to "900"<br>- Under: "**During the study**" references to chemotherapy randomization vs surgical randomization have been deleted and where appropriate references to randomization to surgery have been added.<br>- Under: "**You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.**" This section has been re-organized to reflect the changes to the protocol.<br>- Under: "**Study Plan**" the possible chemotherapy choices are listed; with and without bevacizumab.<br>- Under:" HOW LONG WILL I BE IN THE STUDY?" The section has been changed to reflect the changes to the protocol.<br>-Under: "WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY? "If you are assigned treatment containing bevacizumab" has been changed to: "If you and your doctor choose treatment…"<br>- Under: "**GENERAL INFORMATION ABOUT THE COLLECTION AND USE OF SPECIMENS FOR RESEARCH**" and "**SPECIFIC INFORMATION FOR THIS RESEARCH STUDY**" language has been changed to reflect the fact that the patients must be candidates for surgery. |
| Appendix III | - Specimen Procedures for GOG-0213 have been updated with instructions to use the new Kit Management Application. |

Please update all copies of the protocol at your institution with these changes. **Do not discard the old version. Please retain a copy of earlier versions of the protocol in your regulatory binder as historical documentation.**

**FOR YOUR CONVENIENCE, AND TO FACILITATE LOCAL IRB REVIEW, A COPY OF THE PROTOCOL AND INFORMED CONSENT WITH ALL CHANGES TRACKED ARE BEING POSTED INADDITION TO THE CLEAN VERSIONS.**

Philip J. DiSaia, M.D.
*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES, AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: OCTOBER 1, 2012

RE: PROTOCOL GOG-0213, REVISION # 10

**Protocol Title:** A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version Date: August 9, 2012***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; rcoleman@mdanderson.org**

**IRB Review Recommendation:**

( ) **No review required**
( ) **Expedited review; however, site IRB requirements take precedence***
**(X) Full board review**

***For the studies affected by this Action Letter, CTEP considers all the proposed protocol and informed consent changes to minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the IRB Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor.**

---

We have chosen to broaden the chemotherapy options on GOG-0213 in light of a recently completed and reported phase III study where the combination of gemcitabine, carboplatin and bevacizumab was compared to gemcitabine and carboplatin.(new REF: Aghajanian C, Blank SV, Goff BA, et al., OCEANS: A Randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012; Apr 23, ePub ahead of print)

This trial demonstrated further enhancement in progression-free survival (12.4 mos vs 8.4 mos, HR 0.48, 95% CI:0.39-0.61), response rate (79% vs 57%, p<0.0001) and duration of response (10.4 mos vs 7.4 mos, 95% CI: 0.41-0.70). Although immature at the time of reporting, there was no overall survival benefit with nearly 50% of events recorded.

The following changes have been made and will become effective October 1, 2012:

| | | |
|---|---|---|
| Title Pages | - | Gemcitabine has been added to the title. |
| | - | NCI Version date has been updated. |
| | - | Includes Revisions 1-10 has been updated. |
| | - | Revised has been added to the footer. |
| Schema | - | Has been updated to include the allowance of gemcitabine. Paragraph added at the end of Schema regarding new post surgical randomization treatment options. |
| Table of Contents | - | Page numbering has been updated. |
| Section 2.3 | - | "Gemcitabine" added in first bullet as an additional non-platinum novel agent. |
| | - | "/Taxane" deleted from third bullet. |
| | - | Fourth bullet has been added with new information on combination chemotherapy. |
| Section 2.7 | - | New information on combination therapy that includes gemcitabine has been added mid-section. "...or carboplatin/gemcitabine/bevacizumab" has been added to the last sentence in the section. |
| Section 4.5 | - | Standard gemcitabine drug information has been inserted and subsequent section "Pathology Requirements" has been renumbered. |
| Section 5.23 | - | Chemotherapy treatment arms have been added to include the gemcitabine regimens. **Bolded** text has been added, "...the systemic treatment, which consists of either paclitaxel+carboplatin (as described for arms I and III) or **gemcitabine+carboplatin (as described for arms V and VII) or** paclitaxel+carboplatin+bevacizumab (as described for arms II and IV) **or gemcitabine+carboplatin+bevacizumab (as described for arms VI and VIII)** is selected and declared prior to enrolling onto the study." |
| | - | "or gemcitabine" has been added throughout. |
| Section 5.231 | - | Table has been expanded to include gemcitabine regimens. |
| Section 5.233 | - | Fourth bullet has been added to include drug administration information for gemcitabine. |

- In the fifth bullet, carboplatin infusion time has been changed from 30 to 60 minutes.

Section 5.234 - In the second paragraph the following **bolded** text has been added, "It is recommended that the preparatory regimen…should be given **30 minutes if IV or** 60 minutes **if PO** before infusion to reduce the risk…"

Section 5.235 - Antiemetic Regimens: the second bullet Granisetron **1 mg** has replaced 10mcg/kg.
- **plus dexamethasone 10 mg IV** has been added.
- Third bullet has been added.

Section 5.239 - "Dosing of Gemcitabine- See Section 5.233" has been added.

Section 5.24 - **Arms V and VII** have been added to the duration of Paclitaxel and Carboplatin treatment. "**or Gemcitabine**" has been added.

Section 5.25 - **Arms VI and VIII** have been added to the duration of Carboplatin, Bevacizumab, and Paclitaxel treatment. "**or Gemcitabine**" has been added.

Section 6.18 - Dose modifications for Gemcitabine: Carboplatin **(Arms V, VI, VII, VIII)** have been added.

Section 7.1 - Arms VI, VIII have been added to the table heading.

Section 11.12 - Gemcitabine with Carboplatin (GC) regimen has been added. Subsequent sections have been renumbered.

Section 11.14 - Gemcitabine with Carboplatin and Bevacizumab (GCB) regimen has been added.

Section 11.16 - "GC, GCB" has been added to reflect the new treatment arms in the middle of the paragraph.

Section 11.3 - In the paragraph *Statistical Power- evaluating the efficacy of surgical cytoreduction*, "vs CG vs CGB" has been added.

Section 12. - Reference 73 has been added.

Informed Consent
- "Gemcitabine" has been added to the title.
- NCI Version date has been updated.
- Gemcitabine has been added through-out as an additional option other than paclitaxel.
- In the section, **Study Plan,** table and schema have been updated to show addition of gemcitabine option.
- In the section, **What Side Effects or Risks Can I Expect From Being in the**

**Study?** Gemcitabine and its side effects have been added.

In addition the following changes have been made to agree with Amendment #6. These sections were overlooked when we amended at that time.

Section 3.33 - "This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab." has been added.

Section 3.36 - "This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab." has been added.

Section 3.37 - "This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab." has been added.

Section 3.38 - "This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab." has been added.

Section 3.39 - "This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab." has been added.

Section 7.1 - Asterisk footnote has been added to the table to distinguish bevacizumab specific criteria, due to fact that after 8/29/11 patients elect whether or not to receive bevacizumab at the time of registration.

Section 11.3 - In the paragraph *Interim Analyses* the following **bolded** text has been added to the first sentence, "Interim analyses are planned when there are at least 110 deaths reported among all those patients **randomly** allocated **(prior to August 29, 2011)** to the CT regimen…"

There were no changes to the Appendices.

**Philip J. DiSaia, M.D.**
*Group Chair*

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**Mary C. Sharp**
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES, AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: OCTOBER 1, 2012

RE: PROTOCOL GOG-0213, REVISION # 10 Memo rebroadcast 10-2-12

**Protocol Title:** A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #7921)

***NCI Version Date: August 9, 2012***

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; rcoleman@mdanderson.org**

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( ) **No review required**
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There were no changes to the Appendices.

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Mary C. Sharp
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: AUGUST 12, 2013

RE: PROTOCOL GOG-0213 – REVISION # 11

**Protocol Title:** "A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)"

NCI Version July 8, 2013

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision, and the rationale for the decision, in your study files.

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**Mary C. Sharp**
Chief Financial Officer

# SUMMARY OF CHANGES

For Protocol Revision #11 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: July 12, 2013
Protocol Date: August 19, 2013

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1 | NCI version date is now July 12, 2013.<br>Includes Revisions #1-11.<br>Paula Rogers has replaced Maria Jung as the nurse contact.<br>Revised footer has been added. |
| 3 | TOC | 4-6 | The table of contents has been renumbered and hyperlinked per NCI requirement.<br>"SUGGESTED PATIENT INFORMATION/INFORMED CONSENT" has been deleted. |
| 4 | App. I-V | 106-129 | Appendices have been added to the end of the document per NCI requirement. |
| 5 | IC | | The NCI Version Date is now July 12, 2013. |

## SUMMARY OF CHANGES

For Protocol Revision #11 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: July 12, 2013
Protocol Date: August 19, 2013

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title | 1 | NCI version date is now July 12, 2013. |
| 2. | Quality of Life | 5 | Under Study Plan the schema has been corrected to agree with the version in the protocol. |

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TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: SEPTEMBER 29, 2014

RE: PROTOCOL GOG-0213 – REVISION # 12

**Protocol Title:** "A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)"

NCI Version June 23, 2014

**Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org**

**IRB Review Recommendation:**

**( ) No review required**
**(X) Expedited review; however, site IRB requirements take precedence**
**( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information**

*Although there is modified risk information for bevacizumab, CTEP has indicated that **the added risks are very similar to or associated with risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD).** In this case, (1) watering eyes is associated with allergic rhinitis; (2) wound complication is a more general term and includes wound dehiscence; (3) dehydration is associated with other known AEs such as colitis, nausea, and vomiting; (4) infections, other (necrotizing fasciitis) is a specific type of infection, a previously identified risk; (5) an increase in frequency of neutrophil count decreased resulted in this risk being moved from less likely to likely, but this risk was previously identified; (6) an increase in frequency of platelet count decreased resulted in this risk being moved from reported but undetermined to less likely, but this risk is associated with bone marrow suppression which is already reflected in the increase in frequency of neutrophil count decreased.

**When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised informed consent**

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**document is reviewed and approved by the Investigational Review Board (IRB).** For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the informed consent; however, changes to the ICDs cannot be implemented until they are approved by the IRB. **Please note that there will be no Action Letter.**

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# SUMMARY OF CHANGES

The following changes are being submitted in response to an RA from Dr. Helen Chen (Helen.chen@nih.gov):

For Protocol Revision #12 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: June 23, 2014
Protocol Date: June 23, 2014

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1 | NCT# 00565851 has been added.<br>NCI version date has been updated.<br>Includes Revisions #1-12.<br>Lead Institution and Participation Organizations have been added.<br>Heather Lankes has replaced Kathleen Darcy as Translational Research Scientist.<br>Revised footer has been added. |
| | 4.36 | 32-37 | A Revised CAEPR (Version 2.3, August 1, 2013) has been inserted.<br>• Added New Risk:<br>  • Less Likely: Dehydration; Wound complication<br>  • Rare But Serious: Infections and infestations – Other (necrotizing fasciitis)<br>  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (tympanic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyramidal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular pucker); Eye disorders – Other (transient increased IOP > or = 30 mm Hg); Eye disorders – Other (vitreous hemorrhage); Eye pain; |

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| # | Section | Page(s) | Change |
|---|---|---|---|
| | | | Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperthyroidism; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor pain; Typhlitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain<br>• Increase in Risk Attribution:<br>  • Changed to Likely from Less Likely: Neutrophil count decreased<br>  • Changed to Less Likely from Reported But Undetermined: Platelet count decreased<br>• Decrease in Risk Attribution:<br>  • Changed to Reported But Undetermined from Less Likely: Vertigo<br>• Provided Further Clarification:<br>  • Supraventricular tachycardia is now reported as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, "Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter."<br>  • Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the following footnote (#10) was added, "Anastomotic leak may include Gastrointestinal anastomotic leak; |

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| # | Section | Page(s) | Change |
|---|---|---|---|
| | | | Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak."<br>• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:<br>  • Added: Dehydration; Platelet count decreased; Wound complication<br>• Deleted Risk:<br>  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothorax |
| 2 | 5.1 | 44 | This section has been updated with OPEN language for patient entry and registration. |
| 3 | 10.1-10.3 | 77-85 | References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol. |
| | ICD | | Additional changes have been made to the IC document. |

The following changes are being submitted in response to an RA from Dr. Helen Chen (Helen.chen@nih.gov):

SUMMARY OF CHANGES

For Protocol Revision #12 to: GOG-0213

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: 06/23/2014
Protocol Date: 06/23/2014

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1 | *Title* | 1 | • NCI Version Date has been updated. |
| 2 | *What side effects or risks can I expect from being in the study?* | 12-13 | The possible side effects of Bevacizumab have been updated and now appear in the "condensed risk profile" format.<br>Added new risk:<br>• Occasional: Dehydration; Delay in healing of wounds or spontaneous opening of wounds<br>• Rare: Flesh-eating bacteria syndrome, an infection in the deep layers of skin<br>Decrease in Risk Attribution:<br>• Changed to Reported But Undetermined from Less Likely (i.e., removed from the Risk Profile): Feeling of spinning or whirling. |

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# SUMMARY OF CHANGES

For Protocol Revision #14 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: May 28, 2015
Protocol Date: May 28, 2015

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1-2 | NCI version date has been updated.<br><br>Includes Revisions #1-14.<br><br>Revised footer has been added. |
| 2. | Title Page | 1-2 | The nurse contact has been updated to Anne Heugel. |
| 3. | IC | | NCI version date has been updated. |
| 4. | IC | | "Description of the interim analysis report" has been added. |

SUMMARY OF CHANGES

For Protocol Revision #14 to: GOG-0213

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: May 28, 2015
Protocol Date: May 28, 2015

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1 | *Title* | 1 | NCI Version Date has been updated. |
| 2 | *During the study* | 4-5 | "Description of the Interim Analysis Report" has been added. |

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# SUMMARY OF CHANGES

For Protocol Revision # 15 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: Aug 31, 2015
Protocol Date: Aug 31, 2015

Attached is NCI approved amendment to GOG-0213. This phase III trial includes two distinct components. The first component is to determine whether the addition of bevacizumab to standard platinum-paclitaxel treatment decreases the death rate in women with recurrent, platinum-sensitive ovarian cancer. That component of the trial has been completed and the results have been publically released. The second component of this trial is to assess whether cytoreductive surgery decreases the death rate in women with recurrent platinum-sensitive ovarian cancer. The target enrollment for this component of the study is currently 360 patients and there have been 354 patients enrolled as of Aug-01-2015. The trial is currently enrolling approximately 6 patients per month. This component of the study is currently at 30% of its total information time.

This amendment is to increase the target total enrollment by 125 patients. At the previous recruitment rate the amended enrollment period would be expected to complete in Spring 2017.

The purpose of this amendment is to decrease the time until study maturity. If the target sample size were not increased, then the expected date for study maturity would be mid-2021 to early 2022. If the sample size is increased by 125 patients then the expected date of study maturity is late in the first quarter 2019

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1 | Title Page | 1 | NCI version date has been updated.<br>Includes revisions #1-15.<br>Revised footer has been added. |
| 2. | 11.3 | 89-90 | Increased target sample size for the surgical component of this study. |

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| # | Section | Page(s) | Change |
|---|---|---|---|
| 3. | 11.4 | 93 | Updated the estimated power for the quality of life endpoint due to the altered sample size. |
| 4. | IC | | Updated version date and the number of individuals who will take part in the surgical component of this study. |