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Translational Research in the Gynecologic Oncology Group: Evaluation of Ovarian Cancer Markers, Profiles and Novel Therapies

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Abstract

Objectives—To review the translational research (TR) performed in the Gynecologic Oncology Group (GOG) to evaluate ovarian cancer markers, profiles and novel therapies.

Methods—Prospective trials with stand alone or embedded TR objectives involving patient and specimen accrual as well as retrospective studies using banked specimens and resources were and continue to be performed in the GOG. Appropriate statistical methods are employed to evaluate associations with clinical characteristics and outcomes including tumor response, adverse events, progression free survival and overall survival.

Results—Highlights are presented for some of the collaborative and multidisciplinary TR conducted with the GOG to evaluate markers, pathway and novel therapeutics in epithelial ovarian, primary peritoneal and/or fallopian tube cancer. For example, in GOG 111, high immunohistochemical (IHC) expression of cyclin E was associated with a shorter median survival (29 versus 35 months) and an increased risk of death (hazard ratio [HR]=1.4, 95% confidence interval [CI]=1.0–2.1, p=0.05). In GOG 114/132, non-detectable immunoblot expression of maspin was associated with debulking status (p=0.034) and an increased risk of disease progression (HR=1.89, 95% CI=1.04–3.45, p=0.038) and death (HR=1.99, 95% CI=1.07–3.69, p=0.030) while high CD105-microvessel density (MVD), but not CD31-MVD in tumor was associated with increased risk of disease progression (HR=1.873, 95% CI=1.102–3.184, p=0.020) but not death. In GOG 172, low IHC expression of BRCA1 was associated with advanced stage (p<0.001), serous histology

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PRECIS

Advances in molecular oncology and personalized medicine for women with epithelial ovarian cancer are being realized through the evaluation of markers, pathways and novel therapies.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest except that Dr. Darcy is an employee of the Gynecologic Oncology Group and the organization receives funding from various organizations including the Cancer Therapy Evaluation Program, the National Cancer Institute at the National Institute of Health and Industry collaborators who participated in and/or sponsored the protocols reported in this review.

(p<0.001) and a reduced risk of disease progression (HR=0.64, 95% CI=0.42–0.96) and death (HR=0.51, 95% CI=0.32–0.83) while the CA/AA versus CC genotypes in C8092A in ERCC1 were associated with an increased risk of disease progression (HR=1.44, 95% CI=1.06–1.94, p=0.018) and death (HR=1.50, 95% CI=1.07–2.09, p=0.018).

Conclusions—The GOG has an extensive TR program that provides clues regarding the molecular and biochemical mechanisms of disease, treatments and outcomes in women with or at risk for a gynecologic malignancy.

Keywords

Ovarian Cancer; Markers; Profiles; Tumor Biology; Novel Therapies; Translational Research

INTRODUCTION

Translational research (TR) is the bridge between clinical research and basic science that provides clues regarding the molecular and biochemical mechanisms of disease, treatments and outcomes in clinical trials, and the rationale for integrating advances in oncology, science, technologies and drug development into clinical trials and practice. Given the plethora of agents and modalities available for testing in clinical trials, coordinated and collaborative approaches are needed to move the most promising regimens through the drug development process as rapidly and efficiently as possible. Issues like costs, reimbursements and access must also be considered during the drug development process as it is not sufficient to define new standards of care if the more effective treatments can not be adopted into the continuum of clinical practices in the community.

The Gynecologic Oncology Group (GOG) is a multidisciplinary and international Cooperative Trial Group with a TR program that evaluates markers and profiles with potential diagnostic, prognostic and predictive value in prospective trials involving patient and specimen accrual as well as retrospective studies using banked specimens and resources. The GOG recognizes that TR is a critical element of cooperative group clinical trials in the 21st century and the success of these studies requires the integration of objectives that are scientifically-sound and hypothesis-based; standard operating procedures and training that permit member institutions to submit high quality data and specimens; experienced and funded laboratories with appropriate expertise and validated conventional and high through-put assays; and an infrastructure with well-annotated specimens and resources for cutting-edge TR that improves clinical management, outcomes and quality of life. This review starts with overviews about cancer biology, signal transduction and cancer therapeutics and then provides highlights of some of the collaborative and multidisciplinary TR conducted with the GOG to evaluate markers, pathway and novel therapeutics in ovarian, primary peritoneal and/or Fallopian tube cancer. Ultimately, GOG phase II and III trials will selectively treat and manage patients based on markers and profiles, and personalized medicine will become the new standard of care for women with gynecologic malignancies.

Cancer Biology

The Cancer Genome Atlas (TCGA) project in ovarian cancer is beginning to release data that is confirming that epithelial ovarian cancers (EOCs) exhibit extensive molecular heterogeneity with alterations in numerous pathways including oncogenes, tumor suppressors, cell cycle regulation and DNA repair. EOCs exhibit aneuploidy, chromosomal alterations, genomic instability, mutations, amplifications, overepxression, amplifications, silencing, modifications, splicing and epigenetic mechanisms as well as natural and induced sequence variations. Genomic and epigenetic alterations not only drive tumorigenesis, invasion, metastasis and disease progression, but also affect which patients will or won't respond to specific treatments

or experience adverse events. Among the hundreds of defects and alterations observed within the tumors in individual patients with EOC, most are likely passengers while only a fraction are species-specific operators (drivers). Identification of the casual drivers in individual EOC patients will enable us to design more effective marker-driven clinical trials that select the right drugs for the right patients.

Although the molecular classification of EOC clearly represents a landmark advance for women with a diagnosis of EOC or increased risk of this disease, the more challenging work lies before us. Effective treatments with long-term clinical benefit will not only require sustained inactivation or re-control of the critical drivers of tumorigenesis operating in a particular cancer patient but must also anticipate and counteract natural feedback loops, redundant and divergent genes and pathways as well as innate and acquired resistance mechanisms that are differentially induced in select EOC patients. This includes drug efflux, metabolism, detoxification, clearance along with DNA repair pathways, expression, post-translational modifications, silencing, alternative splicing, isoform-switching and epithelial-mesenchymal transitioning, for example. It is also becoming clear that a number of the molecular defects and mechanisms operative in EOC vary more by cell type and grade than by disease site. A number of clinical trials are already focusing eligibility criteria on select histologies within or across disease sites.

Signal Transduction

Tumorigenesis, invasion, metastasis and disease progression can be controlled of membrane-bound, cytoplasmic and nuclear receptors that can be activated by ligands. Following activation, receptors dimerize or oligiomerize and undergo conformational changes, autophosphorylation and phosphorylation of signaling molecules that ultimately regulate transcription, translation, and post-translational modifications as well as processes affecting cell proliferation, maturation, contact, adhesion, migration, invasion, survival, resistance, and the production and secretion of growth factors, cytokines, chemokines and soluble receptors (Figure 1A and 1B). These autocrine, paracrine and systemic factors then affect different cells in the tumor microenvironment and distant sites thus further regulating cancer progression, angiogenesis, vasculogenesis, permeability, immune function as well as the efficacy and toxicities associated with cancer treatments.

Inappropriate receptor activation promotes tumorigenesis and can be induced by a number of mechanisms including overexpression of autocrine and paracrine factors. Receptors can also be mutated causing constitutive activation in the absence of ligand binding, or be overexpressed via gene amplification, transcriptional activation or post-transcriptional mechanisms which typically require ligand availability and binding for activation. Cross talk between different receptor super families can also activate receptors by a ligand-independent mechanism. Cancer progression, invasion and metastasis are promoted by the amplification, mutation or overexpression of signaling molecules downstream from receptors. Various cell types within the tumor microenvironment can be induced to secrete pro-inflammatory factors that stimulate the vasculature to recruit leukocytes to the tumor. After activation, these tumorassociated leukocytes can release factors that recruit more inflammatory cells and stimulate angiogenesis and neovasculogenesis to sustain tumor growth, promote disease progression, and facilitate tumor invasion and metastasis. Schematics are provided for p53 (Figure 1C), cell cycle regulation (Figure 2A), effects of genotoxic stress (Figure 2B), nucleotide excision repair (Figure 2C) and BRCA1 (Figure 2D) as these pathways are the subject of a number of TR studies conducted by the GOG.

Cancer Therapeutics

Insights into the molecular and biochemical mechanisms operative in cancer development, progression and metastasis have uncovered a wide array of molecules in tumor cells and/or the tumor microenvironment including stromal cells, endothelial cells, endothelial precursor cells, pericytes, and immune cells that can be targeted therapeutically. Among these agents are the molecular targeting therapies that inhibit receptor tyrosine kinases, non-receptor tyrosine kinases, serine/threonine kinases, transferases, proteases as well as other enzymes, processes and/or pathways. Some of the molecular targeting therapies are selective inhibitors while others are dual inhibitors or multiple inhibitors (Table 1). Figures 1A and 1B provide a few examples of molecular targeting agents that can inhibit epidermal growth factor (EGF), EGF receptor (EGFR)$^{ErbB1/Her1}$, ErbB2^{Her2}, vascular endothelial growth factor-A (VEGF-A), VEGF receptor (VEGFR) or downstream signaling molecules. A number of these agents are being evaluated in human EOC and specifically in GOG clinical trials as illustrated in Figures 1A and 1B. In addition to the molecular targeting agents, there is an arsenal of traditional cytotoxic anticancer drugs (Table 2). Alkylating agents and microtuble inhibitors have been particular effective in EOC. Despite high initial response rates to first-line treatment and re-challenge with platinum agents and taxanes, about 30% of women with advanced stage EOC fail to respond to initial platinum-taxane based chemotherapy and 5-year survival remains below 40% for women with advanced stage EOC who underwent surgical staging and cytoreduction.

TR IN PHASE III PROTOCOLS

See below for highlights of some of the retrospective and prospective TR conducted in GOG phase III ovarian, primary peritoneal and/or Fallopian tube protocols that have completed accrual.

GOG 111 Protocol

GOG 111 was a Cancer Therapy Evaluation Program (CTEP)-sponsored, randomized phase III protocol by McGuire and colleagues that showed improvements in response rate (p=0.01), progression-free survival (PFS, p<0.001) and overall survival (OS; p<0.001) following intravenous paclitaxel and cisplatin compared with intravenous cyclophosphamide and cisplatin in women with previously-untreated, histologically-confirmed, suboptimal stage III EOC who underwent surgical staging and had >1 cm residual disease or stage IV EOC (Table 3) [1]. Birrer and colleagues initiated a series of retrospective studies to evaluate the prognostic relevance of a panel of markers including cell cycle regulators [2], the p53 tumor suppressor gene [3] and several proto-oncogenes including ErbB2^{Her2} [4] and cMYC [5] in archival formalinfixed and paraffin-embedded (FFPE) primary tumor specimens from women with advanced stage who participated in the GOG 111 protocol.

High cyclin E protein expression, defined as >40% cyclin E positive tumor cells, was associated with a shorter median survival (29 versus 35 months) and an increased risk of death (hazard ratio [HR]=1.4, 95% confidence interval [CI]=1.0–2.1, p=0.05) [2]. This association was most notable in women with stage III disease (HR=1.7, 95% CI-1.1–2.6, p=0.03), serous histology (HR=1.8, 95% CI=1.2–2.8, p=0.01) and non-measurable disease (HR=2.4, 95% CI=1.4–4.3, p<0.01) and those randomly allocated to paclitaxel and cisplatin (HR=1.8, 95% CI=1.1–2.9) [2]. Amplification of *cyclin E*, detected by fluorescence in situ hybridization (FISH), was shown to be associated with high verse low cyclin E expression (p<0.006) [2]. Investigations are currently underway to evaluate the clinical utility of tumor expression of p27, cyclin D1 and p57 in the GOG 111 cohort (Table 3). Overexpression of p53, defined as ≥10% tumor cells exhibiting nuclear staining using the N-terminal DO-7 antibody (Figure 1C), was associated with GOG performance status (p=0.018) and grade (p=0.003), but not with PFS or OS [3]. *ErbB2^{Her2}* amplification, defined by FISH as >2 or >4 copies of *ErbB2^{Her2}*/chromosome 17,

was a rare event in EOC and was not associated with clinical characteristics, tumor characteristics or any measure of outcome including PFS or OS [4]. In addition, *cMYC* amplification, defined by FISH as ≥1.5 or ≥2 copies *cMYC*/chromosome 8, was not associated with clinical characteristics, tumor characteristics, PFS or OS [5]. Polysomy 8 was observed in 22 patients without *cMYC* amplification and 3 with *cMYC* amplification, and was associated with age and measurable disease status, but not other clinical covariates or outcomes [5].

GOG 114/132 Protocols

Berchuck and colleagues at Duke University Medical Center initiated a series of retrospective studies to evaluate the prognostic relevance of a panel of tumor suppressors, angiogenic markers, cell cycle regulators, transcriptional regulators and DNA repair proteins in frozen and archival FFPE primary tumor specimens available from women with advanced stage EOC who participated in the GOG 114 or the GOG 132 protocol. GOG 114 was a CTEP-sponsored, intergroup, randomized phase III trial with the Southwestern Oncology Group (Protocol 9227) and the Eastern Cooperative Oncology Group (Protocol GO114) by Markman and colleagues which showed improvements in PFS (p=0.01) and OS (p=0.05) with high-dose intravenous carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin compared with intravenous paclitaxel and cisplatin in women with previously-untreated, histologically-confirmed, optimally-resected, stage III EOC who underwent surgical staging and had <1 cm residual disease (Table 3) [6]. GOG 132 was a CTEP-sponsored, randomized phase III trial by Muggia and colleagues which demonstrated that inferior response rates (p<0.001) and PFS (p<0.001) but similar OS were observed with paclitaxel monotherapy compared with either cisplatin monotherapy or the paclitaxel and cisplatin combination in women with previously-untreated, histologically-confirmed, suboptimally-resected stage III and stage IV EOC who underwent surgical staging and had >1 cm residual disease (Table 3) [7].

A mutation in exons 2 to 11 of the multifunctional tumor suppressor, *p53*, was associated with non-mucinous or clear cell histologies (p=0.018) and a short-term reduction in the risk of disease progression (HR=0.4, 95% CI=0.2–0.8, p=0.014) and death (HR=0.3, 95% CI=0.1–0.8, p=0.014) [8]. These striking risk reductions were time-dependent and eventually disappeared around three years following initiation of primary treatment [8]. Overexpression of p53, defined as tumors with any detectable p53 immunostaining using the N-terminal DO-1 antibody (Figure 1C), was observed in 55 patients (100%) with only missense mutation(s), seven patients (32%) with truncation mutations, and eight patients (40%) lacking a mutation in exons 2 to 11, and was associated with tumor grade (p0.018) but was not associated with PFS or OS [8]. Maspin, another tumor suppressor, was not detected by immunoblot analysis in 19 (28%) of the frozen primary tumors tested, and non-detectable maspin was associated with suboptimally-debulked disease (p=0.034) and an increased risk of disease progression (HR=1.89, 95% CI=1.04–3.45, p=0.038) and death (HR=1.99, 95% CI=1.07–3.69, p=0.030) [9]. Follow up studies are underway to determine if loss of maspin expression was associated, at least in part, to methylation-induced epigenic silencing [10]. Associations were observed between categorized immunoblot expression of the pro-angiogenic factor, VEGF-A, and p53 overexpression (p=0.022), VEGFR-1 and either race (p=0.027) or histologic subtype (p=0.007), and thrombospondin-1 (an angiogenic inhibitor and promoter) and either PFS (HR=2.19, 95% CI=1.29–3.71, p=0.004) or OS (HR=1.93, 95% CI=1.12–3.32, p=0.018) [11]. High CD105 microvessel density (CD105-MVD), defined as ≥19.25 CD105 positive vessels per high density field, was associated with increased risk of disease progression (HR=1.873, 95% CI=1.102–3.184, p=0.020) but not death, whereas CD31-MVD, defined as ≥24.25 CD31-positive vessels per high power field, was not associated with PFS or OS [12]. In the GOG 114/132 cohort, none of the cancers exhibited homozygous deletions in p16, but loss of immuno-expression of p16 was associated with wild-type versus mutant p53 (p=0.03) and Rb expression (p<0.001) [13]. Investigations are currently underway to determine the

optimal combination of G_1 stimulators (cyclin D1, cyclin E, cdk4, Ki67) and inhibitors (p16, pRb, p27, p14) with clinical factors that predicts PFS and OS in the GOG 114/132 cohort [14]. Relative immunoblot expression of the p63 isoform lacking the transactivation domain, ΔNp63α (a homolog of p53), was associated with debulking status (p=0.023), relative expression of VEGF-A (p=0.045), and an increased risk of disease progression (HR=1.483; 95% CI=1.060–2.076; p=0.021) but not with p53 status or survival [15]. Panasci and colleagues are currently examining the prognostic relevance of x-ray repair cross-complementing protein group 3 (XRCC3), a member of RecA / RAD51-related protein family that interacts with RAD51C and is involved in DNA repair and homologous recombination to maintain chromosome stability, in the GOG 114/132 cohort.

GOG 148 Protocol

GOG 148 (Table 3) was a CTEP-sponsored, serum marker protocol by Burger and colleagues which demonstrated that among women who participated in a randomized phase III protocol for early stage EOC (GOG 95 or 157) or advanced stage EOC (GOG 111, 114, 132, 152 or 162) and had either low or high CA 125 levels, those with high sTNFR-I and low sTNFR-II levels had the lowest risk, patients with low sTNFR-I and sTNFR-II or high sTNFR-I and sTNFR-II levels had an intermediate risk, and patients with low sTNFR-I levels and high sTNFR-II levels had the highest risk of disease progression [16]. The prognostic value of serial assessment of these soluble death receptors in women with low and high CA125 is currently under investigation.

GOG 157 Protocol

GOG 157 was a CTEP-sponsored, randomized phase III trial by Bell and colleagues which demonstrated that a 6 versus 3 cycle regimen of paclitaxel and carboplatin resulted in significantly more frequent grade 3 or 4 neurotoxicity and anemia, and statistically similar PFS and OS in women with previously untreated, histologically-confirmed, completely-resected stage IA grade 3 (or clear cell tumors), stage IB grade 3 (or clear cell tumors), stage IC or stage II EOC who underwent optimal surgical staging (Table 3) [17]. Retrospective studies were also initiated to evaluate the prognostic relevance of p53 [3], cell cycle regulators [18] and angiogenic markers [19] in archival FFPE primary tumors from women who participated in the GOG 157 protocol. Overexpression of p53, defined as ≥10% tumor cells exhibiting nuclear staining using the DO-7 antibody (Figure 1C), was observed in 51% (73/143) of the GOG 157 early stage EOCs and was associated with worse PFS (logrank test: p=0.013), a 2-fold higher risk of disease progression (95% CI=1.15–3.63; p=0.015), and a similar risk of death, but was not a statistically significant independent prognostic factor for PFS (HR=1.81, 95% CI=0.99–3.30, p=0.052) [3]. Investigations are underway to examine the prognostic relevance of the IHC expression of cyclin E and p27 [18] as well as the angiogenic markers: thombospondin-1, angiopoietin-1, SPARC, VEGFR-2 (Flk-1), TIE-2 and VEGF-A [19] in the GOG 157 cohort.

GOG 158 Protocol

GOG 158 was a CTEP-sponsored, randomized phase III trial by Ozol and colleagues which demonstrated that the experimental combination of a 3-hour infusion of paclitaxel followed by carboplatin was less toxic, easier to administer and not inferior in terms of PFS and OS to the control regimen with a 24-hour infusion of paclitaxel followed by cisplatin in women with previously-untreated, histologically-confirmed, optimal-resected stage III EOC who underwent adequate surgical staging and had <1 cm residual disease (Table 3) [20]. The presence of detectable versus undetectable platinum DNA adducts was associated with longer median OS (60.3 versus 36.3 months; p=0.029) and a reduced risk of death (HR=0.607, 95% CI=0.385–0.958, p=0.032) for women with detectable versus undetectable adducts, but was not associated with PFS or an independent prognostic factor for OS [21]. ERCC1 mRNA

expression, categorized as positive versus negative, in post-treatment peripheral blood leukocytes was not associated with either PFS or OS [21].

GOG 175 Protocol

GOG 175 was a CTEP-sponsored, intergroup randomized phase III trial with the Southwest Oncology Group by Mannel and colleagues that will compare PFS, OS and the frequency of adverse events in women with previously-untreated, histologically-confirmed, completely-resected stage IA grade 3 (or clear cell), stage IB grade 3 (or clear cell), stage IC or stage II EOC who were treated with intravenous paclitaxel and carboplatin every 3 weeks for 3 cycles followed by a 1-hour intravenous infusion of 40 mg/m^2 every week for 24 weeks versus observation for 24 weeks (Table 3). Archival tumor specimens recovered from the GOG 175 virtual tissue bank underwent array comparative genome hybridization (aCGH) analysis to compare copy number aberrations (CNAs) in DNA repair genes including the Fanconi anemia complementation group (FANC) and RAD51 families with the rest of the genome [22,23].

GOG 172/182 Protocols

A series of TR studies are leveraging specimens and resources from the GOG 172 and 182 protocols. GOG 172 was a CTEP-sponsored, randomized phase III trial by Armstrong and colleagues which demonstrated that the intraperitoneal versus the intravenous cisplatin and paclitaxel regimen resulted in improvements in PFS (p=0.05) and OS (p=0.03) with 5.5 and 15.9 month longer median PFS and OS, respectively, worse adverse effects (p≤0.001) and quality of life before cycle 4 and 6-weeks after treatment completion, but not 1-year after treatment completion in women with previously-untreated, histologically-confirmed, optimally-resected, stage III EOC who underwent adequate surgical staging and had <1 cm residual disease (Table 3) [24]. GOG 182 was a five arm, CTEP-sponsored, international intergroup phase III randomized trial with Australia and New Zealand GOG, Medical Research Council United Kingdom; Istituto Mario Negri, Southwest Oncology Group, Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, Cancer and Leukemia Group B, National Surgical Adjuvant Breast and Bowel Project and Radiation Oncology Group by Bookman and colleagues which demonstrated that addition of a third cytotoxic agent in a triplet or sequential doublet regimen following optimal or suboptimal cytoreductive surgery for the treatment of advanced stage EOC or PPC provided no added benefit to PFS or OS compared with standard paclitaxel and carboplatin in women with previously-untreated, histologically-confirmed stage III or stage IV EOC or PPC with either optimally-resected disease (≤1 cm residual disease) or suboptimally-resected disease (>1 cm residual disease) following initial surgery (Table 3) [25].

Thus far, mutations in *BRCA1* were identified in DNA extracted from a buffy coat specimen from 16 (5%) of GOG 172 patients [26]. A thorough evaluation of the type and distribution of mutations and common variations observed in *BRCA1* and associations with clinical outcome in the GOG 172 cohort are currently underway. *BRCA1* promoter methylation was observed in specific CpG sites in sporadic EOC including women who participated in GOG 172 and transcript expression of *BRCA1* by RT-PCR was significantly lower in women with a methylated compared with an unmethylated *BRCA1* promoter [27]. Low IHC expression of BRCA1, defined as <10% positive tumor cells, was associated with advanced stage (p<0.001), serous histology (p<0.001), better PFS (p=0.03) and OS (p=0.006), and a reduced risk of disease progression (HR=0.64, 95% CI=0.42–0.96) and death (HR=0.51, 95% CI=0.32–0.83) [28]. Results of additional IHC studies of BRCA1 by route of administration in GOG 172 cases will be presented at the 2010 Society of Gynecologic Oncologist (SGO) Meeting. Denaturing high-performance liquid chromatography, sequence analysis, and single nucleotide polymorphism genotyping by pyrosequencing for the *CHEK2* gene demonstrated that variations in CHEK2 do not appear to make a significant contribution to the pathogenesis of

sporadic EOC in the United States [29]. In the GOG 172 cohort, the codon 118 polymorphism in *ERCC1* was not significantly associated with disease progression or death whereas the C/A or A/A versus C/C genotypes in *C8092A* in *ERCC1* were associated with 6- and 17-month shorter median PFS and OS, respectively, and an increased risk of disease progression (HR=1.44, 95% CI=1.06–1.94, p=0.018) and death (HR=1.50, 95% CI=1.07–2.09, p=0.018) [30]. Subset analysis stratified by treatment regimen demonstrated a distinct PFS and OS advantage for women with the C/C compared with either the C/A or A/A genotypes in *C8092A* in *ERCC1* in women randomly allocated to the IP treatment arm [30]. The associations between codon 118 and C8092A polymorphisms in ERCC1 and PFS and OS in the GOG 182 cohort are under active investigation [31]. Results of an IHC study of ERCC1 in GOG 172 will be presented at the 2010 SGO Meeting. Additional studies are also underway to evaluate the relationship between common polymorphisms in DNA repair genes (*BRCA1* and *BRCA2* [32] as well as *XRCC1*), efflux pumps (*ABCB1*, *ABCC2* and *ABCG2* [33]) and detoxicification enzyme (*GSTρ1*) and measures of clinical outcome including PFS, OS and common severe adverse effects, and to perform genome-wide association studies in the GOG 172 and 182 cohorts.

GOG 198 Protocol

GOG 198 was a CTEP-sponsored, randomized phase III trial by Hurteau and colleagues that evaluated oral daily thalidomide versus tamoxifen and the prognostic relevance of serum VEGF in women with biochemical-recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (Table 3). Investigations are also underway to evaluate the serial changes in VEGF-A during treatment and other angiogenic markers and cytokines in this setting.

GOG 218 Protocol

GOG 218, sponsored by CTEP and Genetech, is a three-arm, randomized, doubleblinded, placebo-controlled phase III trial by Burger and colleagues that will evaluate paclitaxel, carboplatin and placebo plus placebo maintenance versus paclitaxel, carboplatin and bevacizumab plus placebo maintenance versus paclitaxel, carboplatin and bevacizumab plus bevacizumab in women with previously-untreated epithelial ovarian, primary peritoneal or fallopian tube cancer who underwent adequate surgical staging and cytoreduction with FIGO stage III disease with any gross or palpable residual disease or FIGO stage IV disease (Table 3). A series of TR studies are leveraging specimens and resources including those designed to validate published genomic profiles, angiogenic markers, single nucleotide polymorphisms (SNPs), cell-free DNA, EGFR family members/ligands, markers of VEGF-targeted therapy as well as new markers and profiles including those identified by The Genome Atlas Project in ovarian cancer. New discovery and validation efforts are also built into GOG 218 including a number of genomic profiling, SNP and genome-wide association studies.

TR IN DEVELOPMENTAL THERAPEUTICS PROTOCOLS

The GOG has conducted TR in a series of phase II ovarian, primary peritoneal and/or Fallopian tube protocols (sponsor) including the evaluation of capecitabine in GOG 146L (CTEP/Roche Laboratories) [34], bortezomib in GOG 146N (CTEP/Millennium Pharmaceuticals, Inc.) [35], cetuximab and carboplatin in 146P (Bristol-Myers Squibb/Imclone) [36], trastuzumab in GOG 160 (CTEP/Genetech) [37], gefitinib in 170C (CTEP) [38], bevacizumab in GOG 170D (CTEP) [39,40], imatinib in GOG 170E (CTEP/Novartis) [41], sorafenib in GOG 170F (CTEP), lapatinib in GOG 170G (CTEP), temsirolimus in GOG 170I (CTEP), enzastaurin in GOG 170J (Eli Lilly), AMG 706 in GOG 170L (Amgen), dasatinib in GOG 170M (Bristol-Myers Squibb), and A6 in GOG 170N (Angstrom). Results of 170I and 170J will be presented at the 2010 SGO Meeting. Other phase II protocols with TR are in various stages of development and design including the evaluation of AMG 102 in GOG 170P (Amgen),

EGEN-001 in DTM0835 (Expression Genetics), TRC105 in DTM0917 (Tracon Pharmaceuticals), MK-2206 in DTM0926 (Merck) and MK-4827 in DTM-0929 (Merck). Table 1 provides details regarding the mechanism(s) of action of the molecular targeting agents.

ADDITIONAL TR STUDIES

GOG 136 Protocol

GOG 136, is a CTEP-sponsored, specimen banking protocol by Cibull and colleagues for women undergoing a surgery for a gynecologic malignancy or a prophylactic oophorectomy which has supported a number of note worthy studies including those reported by Zorn et al. [42,43] and Beck et al. [44–46].

GOG 143/144 Protocols

The CTEP-sponsored GOG 143 protocol demonstrated that in an unselected, clinic-based series of ovarian cancer cases, 12 patients exhibited protein truncation mutations in *BRCA*1 and another 12 displayed *BRCA1* mutations of unknown significance [47]. GOG 144 was a CTEP-sponsored protocol for women with familial ovarian cancer that screened 26 women for mutations in *BRCA1*/*BRCA2* and detected 12 deleterious alterations; 8 in *BRCA1* and 4 in BRCA2 [48]. Mutations in BRCA1 or BRCA2 were present in about 50% of ovarian cancer patients with at least one first-degree relative with disease, and in 70% of patients with two or more relatives with ovarian/breast cancer (p=0.0002) [48].

GOG 199 Protocol

The GOG 199 protocol is a prospective, international, two-cohort, non-randomized study by Greene and colleagues, in the Clinical Genetics Branch an NCI Intramural Research Program, the GOG, and the Cancer Genetics Network, in women at genetic risk of ovarian cancer, who undergo risk-reducing salpingo-oophorectomy (RRSO) or screening [49]. A series of TR studies leverage specimens and resources from the GOG 199 protocol including GOG 246[CIMBA-4] which demonstrated that the minor allele of the rs3817198 SNP in *LSP1* was associated with increased breast cancer risk only for *BRCA2* mutation carriers (HR=1.16, 95% CI=1.07–1.25, p-trend=2.8×10^{-4}) whereas the rs13387042 SNP at 2q35, but not the rs13281615 SNP at 8q24, was associated with breast cancer risk for *BRCA1* mutation carriers (HR=1.14, 95% CI=1.04–1.25, p=0.005) and *BRCA2* mutation carriers (HR=1.18, 95% CI=1.04–1.33, p=.0079) [50]. In addition, GOG 8008[CIMBA-5] will evaluate the association between SNPs in rs16942 in *BRCA1*, rs2237060 in *RAD50*, *SNP3* and rs2241193 in *IGFBP5* and breast cancer risk in *BRCA1*/*BRCA2* mutation carriers. GOG 8009 and 8010 represent genome-wide association studies examining modifiers of breast cancer risk in *BRAC1 and BRCA2* mutation carriers, respectfully. Additional studies are also under development including CIMBA-6 and CIMBA-7.

FUTURE DIRECTIONS

Release of data from the TCGA project in ovarian cancer is expected to solidify our view of ovarian cancer by defining a comprehensive catalog of the genomic and epigenetic changes in EOC. Translation of these findings into clinical trials and practice will require coordinated efforts that leverage resources, expertise and funding for retrospective and prospective validation studies in well-annotated specimens from independent EOC patients. The GOG offers a variety of mechanisms and unique sets of specimens and resources to translate the TCGA findings into marker-driven phase II and ultimately phase III clinical trials that advance molecular oncology and personalized medicine for women with EOC and establish new standards of care with an arsenal of validated markers and profiles with diagnostic, prognostic and/or predictive value.

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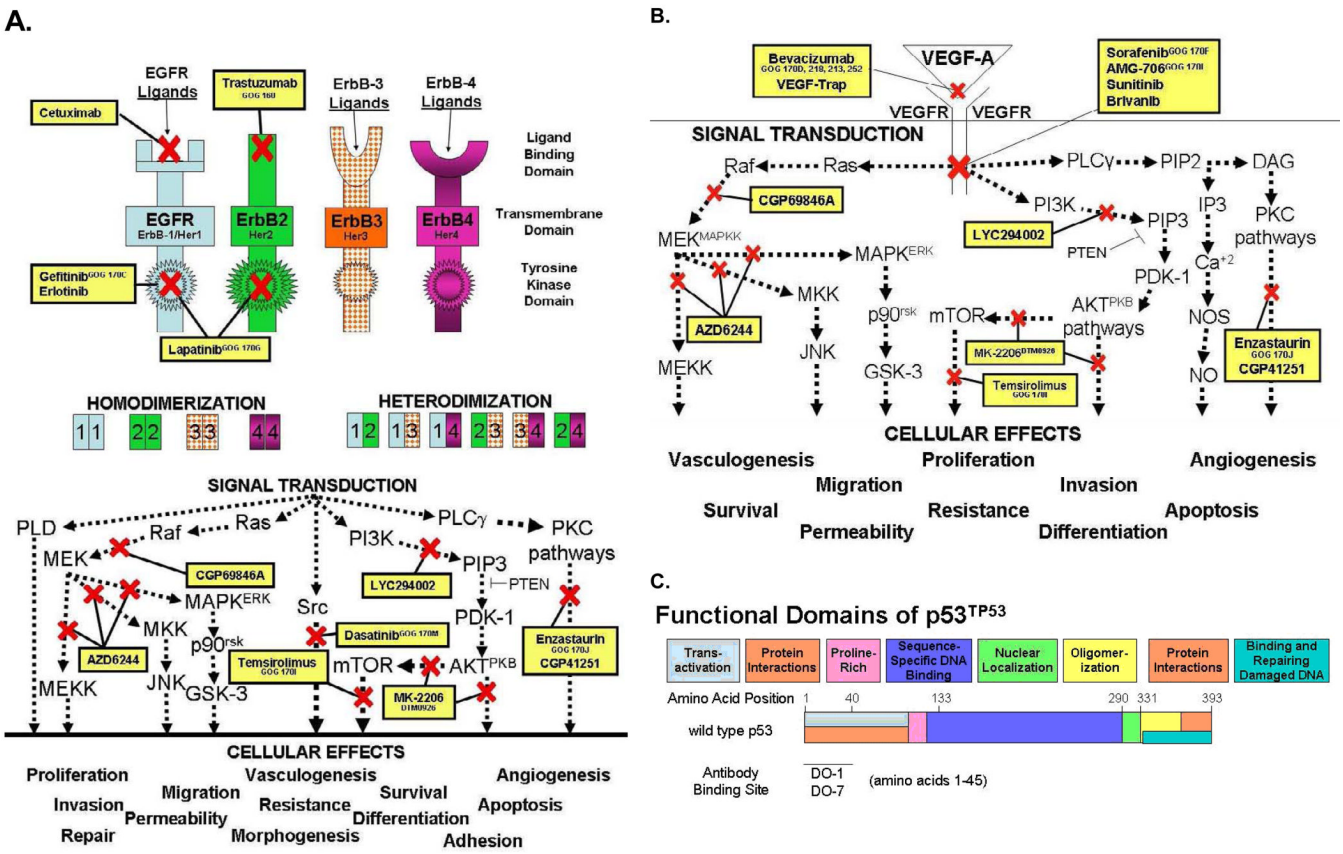

Figure 1.

Panel A provides a schematic representation of ErbB receptor family members and ligands (as referenced by Darcy et al. [51,52]). The ErbB receptor family, composed of epidermal growth factor receptor (EGFR)$^{ErbB1/Her2}$, ErbB2^{Her2}, ErbB3^{Her3} and ErbB4^{Her4}, has an extracellular ligand binding domain, a transmembrane domain and a cytoplamic tyrosine kinase domain. EGFR ligands include EGF, TGFα, HB-EGF, amphiregulin, betacellulin and epiregulin. ErbB2 has very high intrinsic tyrosine kinase activity in the absence of any known ligands. ErbB3 has a very weak tyrosine kinase domain and is activated by heregulins. NRG2, NRG3, heregulins and betacellulin are ligands for ErbB4. Upon binding ligand, the membrane receptor tyrosine kinases undergo conformation changes, dimerization and autophosphorylation which triggers recruitment of substrates and docking proteins, and phosphorylation of substrates. The distinct ErbB receptor homodimers and heterodimers differentially induce a distinct spectrum of signal transduction cascades and cellular effects. Molecular targeting agents are provided in yellow boxes for EGFR, ErbB2 and various downstream signaling molecules including Raf, MEK^{MAPKK}, Src, PI3K, AKT^{PKB}, mTOR and PKC. Panel B provides a schematic illustration of vascular endothelial growth factor receptor (VEGFR) activation by vascular endothelial growth factor-A (VEGF-A) [53] which induces conformational changes, dimerization and autophosphorylation of this membrane receptor tyrosine kinase. Various signal transduction cascades are induced following activation of the VEGFR which regulate cellular effects including cell proliferation, differentiation, survival, apoptosis, migration, invasion, resistance, permeability, angiogenesis and vasculogenesis. Molecular targeting agents are provided in yellow boxes with lines and a red X to indicate the drug target. Panel C illustrates the functional domains of the wild type p53 tumor suppressor with the binding sites for the N-terminal DO-1 and DO-7 monoclonal antibodies against p53 (as referenced by Darcy et al. [3,13]).

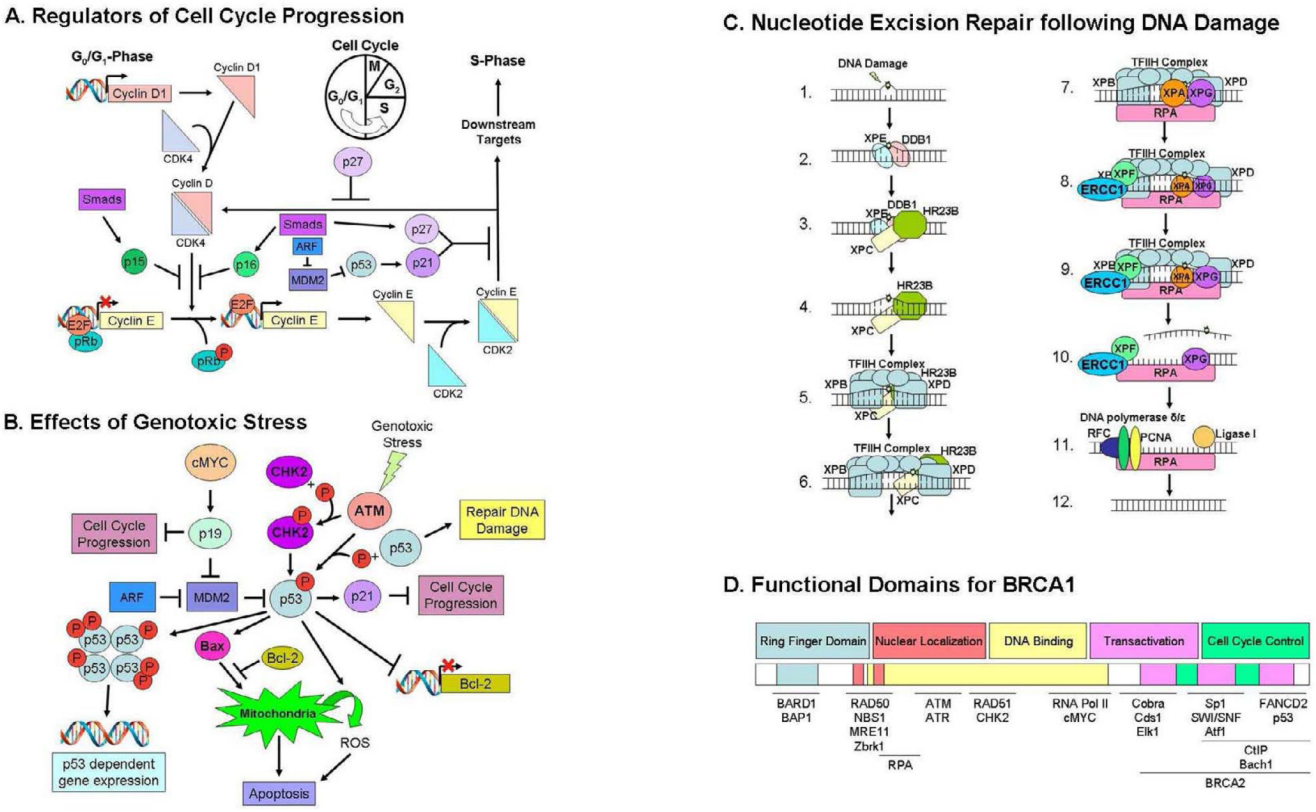

Figure 2.

Panel A depicts some of the regulators of cell cycle progression with emphasis on the transition from G_0/G_1 to S phase of the cell cycle [54]. Panel B illustrates some of the regulators of cell cycle progression, p53-dependent gene expression, apoptosis and DNA repair following genotoxic stress [55]. Panel C provides a schematic representation and brief description of the steps involved in nucleotide excision repair follow DNA damage [56]. Step 1. DNA is damaged by drugs and radiation. Step 2. XPE-DDB1 complex binds to damaged DNA. Step 3. XPE-DDB1 complex assists in recruiting XPC-HR23B. Step 4. XPC-HR23B complex binds directly to the damaged DNA and XPE-DDB1 complex is released. Step 5. TFIIH complex with XPB and XPD binds to the damaged DNA. Step 6. XPB and XPD helicases unwind the DNA helix. Step 7. XPA, RPA and XPG bind sequentially and the XPC-HR23B complex is released and recycled. Step 8. The ERCC1-XPF exonuclease is recruited. Step 9. Incisions are induced on the 5' side (ERCC1) and the 3' side (XPG) of the damaged DNA. Step 10. XPA, TFIIH complex with XPD and XPB, and the oligonucleotide with the damage are removed. Step 11. The resulting gap is filled by a DNA polymerase and RFC, PCNA and ligase I are recruited. XPF-ERCC1 and XPG are displaced. Step 12. DNA is ligated and proteins are released. Panel D illustrates the functional domains within BRCA1 and the general localization of binding sites for a number of the proteins that interact with BRCA1 and are involved in cell cycle regulation, DNA repair and chromatin remodeling [57–59].

Table 1

Molecular Targeting Anti-Neoplastic Agents

Mode of Action of Selective Inhibitors	Agents	
Inhibit vascular endothelial growth factor (VEGF)	bevacizumab	VEGF-trap
Inhibit VEGF receptor (VEGFR)	vatalanib	cediranib
Inhibit epidermal growth factor receptor (EGFR)	gefitinib cetuximab ABX-EGF	erlotinib matuzumab
Inhibit human EGF receptor 2 (Her2) / ErbB2	trastuzumab CP-724,714	SUCI02
Inhibit MEK / mitogen activated protein kinase kinase (MAP2K) / MKK	AZD6244	
Inhibit mammalian target of rapamycin (mTOR) / FK506 binding protein 12-rapamycin associated protein 1 (FRAP1)	rapamycin RAD001	temsirolimus AP23573
Inhibit protein kinase C (PKC) isoforms	brystatin-1	CGP41251
Inhibit PKC-beta	enzastaurin	
Inhibit poly ADP ribose polymerase (PARP)	MK-4827 BSI-201 INO-1001	ABT-888 Olaparib AG140699
Inhibit ATM	LY294002	KU-55933
Inhibit Notch	MK0752	
Inhibit AKT / protein kinase B (PKB)	MK-2206	API-59-OME
Inhibit Src family	PD173956 PD180970	PD173958 AP23846
Inhibit CD105 / endoglin	TRC105	
Inhibit hepatocyte growth factor (HGF)/scatter factor	AMG 102	
Inhibit Janus kinase 2 (JAK2)	cucurbitacin-A	
Inhibit signal transducers and activators of transcription 3 (STAT3)	cucurbitacin-Q	
Inhibit phosphoinositide-3 kinase (PI3K)	LYC294002 ZSTK474	Wortmannin
Inhibit Raf	CGP 69846A	
Inhibit p38 mitogen-activated protein kinase (MAPK) / RK / CSBP	SB203580	
Inhibit Aurora kinases	MK-0457 VX-680	L-001281814
Inhibit cyclin dependent kinase (CDK) pathways	flavopiridol BMS-387032	seliciclib PD 0332991
Inhibit hypoxia-inducible factor-1 alpha (HIF-1alpha)	EZN-2968	
Inhibit cyclooxygenase-2 (COX-2)	celecoxib rofecoxib	valdecoxib
Inhibit 26S proteasome	bortezomib	
Inhibit farnesyl transferase	tipifarnib BMS-214662	ionafarnib L778123
Inhibit matrix metalloproteinases (MMPs)	marimastat	BAY 12–9566

Mode of Action of Selective Inhibitors	**Agents**	
Inhibit urokinase-type plasminogen activator (uPA) system	WX-UK1 Urokinase-derived Peptide A6	WX-671
Inhibit histone deacetylase (HDAC)	vorinostat trichostatin A	valproic acid LBH589
Inhibit heat shock protein 90 (HSP90)	17-allylamino-17-demethoxygeldanamycin	geldanamycin
Inhibit estrogen receptors (ER)	tamoxifen	raloxifin
Inhibit estrogen metabolism	letrazole exemestane	anastrozole
Inhibit progesterone receptors (PR)	provera	depoprovera
Synthetic retinoid	fenretinide	
Mode of Action of Dual Inhibitors		
Inhibit EGFR and Her2 / ErB2	lapatinab	
Inhibit EGFR and VEGFR	ZD6474	AEE788
Inhibit VEGFR and PDGFR	axitinib	vandetanib
Inhibit VEGFR and FGFR	brivanib	CP-547,632
Inhibit VEGF and bFGF	thalidomide	
Inhibit JAK2 / STAT3	cucurbitacin-B cucurbitacin-I	cucurbitacin-E
Inhibit Chk1 and Chk2	AZD-7762	PF-00477736
Mode of Action of Multiple Inhibitors		
Inhibit EGFR, Her2, ErbB3 and ErbB4	canertinib	
Inhibit bcr-abl, c-Kit and PDGFR	imatinib	
Inhibit VEGFR, PDGFR and FGFR	JNJ-17029259	BIBF1120
Inhibit VEGFR, PDGFR and Flt3	SU11657	ABT-869
Inhibit VEGFR, PDGFR and Raf	sorafenib	
Inhibit VEGFR, PDGFR and c-Kit	sunitinib AMG 507 BAY 57–9352	AMG-706 AG-013736
Inhibit VEGFR, PDGFR, c-Kit, CSFR, Flt3 and FGFR	CHIR-258	
Inhibit Bcr-Abl, Src and Ephrins	dasatinib	
Inhibit Akt, FGFR3 and FLT3	benzoylstaurosporin	
Inhibit VEGFR, PDGFR, CDK1 and CDK2	ZK304709	
Inhibit Raf, VEGFR-2, VEGFR-3, PDGFR-beta, FLT3, c-Kit and p38-alpha MAPK	BAY 43–9006	
Inhibit MEK, Erk1 and Erk2	UO126 PD184352	PD98059
Inhibit PKC, Chk1 and Chk2	UCN-01	
Recombinant adenovirus		
Encoding p53	Advexin SCH58500	Gendicine

Table 2

Cytotoxic Anti-Neoplastic Agents.

Mode of Action	Agents	
Alkylate / cross-link DNA	cisplatin cyclophosphamide	carboplatin
Inhibit microtubules	paclitaxel xyotax vincristine	docetaxel vinblastine
Intercalate DNA and inhibit RNA sysnthesis	doxorubicin dactinomycin	daunorubicin thalidomide
Function as a nucleoside analog	gemcitabine	
Damage DNA and prevent repair	bleomycin	
Inhibit DNA synthesis and RNA function	cytarabine	
Inhibit dTMP synthesis	5-fluorouracil	capecitabine
Inhibit purine ring biosynthesis and dTMP synthesis	methotrexate	
Inhibit ribonucleotide reductase	hydroxyurea	
Inhibit purine ring biosynthesis and nucleotide interconvesion	6-mercaptopurine	6-thioguanine
Inhibit pyrimidine biosynthesis	PALA*	azaribine
Inhibit topoisomerase I (TOPO I)	irinotecan camptothecin lamellarin D	topotecan karenitecin
Inhibit topoisomerase II (TOPO II)	etoposide doxorubicin	teniposide

*N-phosphonacetyl-L-aspartate (PALA).

Table 3

TR in Phase III Ovarian, Peritoneal and/or Tubal Protocols Closed to Patient Enrollment

Protocol ID	Patient Population	Treatments	Translational Research (TR)
GOG 111	Women with previously-untreated, histologically-confirmed, suboptimal stage III epithelial ovarian cancer (EOC) who underwent surgical staging and had > 1 cm residual disease or stage IV EOC [1].	Randomized to 750 mg/m^2 intravenous cyclophosphamide and 75 mg/m^2 intravenous cisplatin (1 mg/minute) every 3 weeks for 6 cycles ***versus*** 135 mg/m^2 intravenous paclitaxel as a continuous 24 hour infusion on day 1 and 75 mg/m^2 intravenous cisplatin (1 mg/minute) on day 2 every 3 weeks for a 6 cycles [1].	• Immunohistochemical (IHC) expression of cyclin E and fluorescence in situ hybridization (FISH) for *cyclin E* [2]. • IHC expression of p27 {Farley et al., in progress}. • IHC expression of cyclin D1 and p57 {Hurteau et al., in progress}. • IHC expression of p53 [3]. • FISH for *Her2* and centromere of chromosome 17 (CEP17) [4]. • FISH for *c-MYC* and CEP8 [5].
GOG 114	Women with previously-untreated, histologically-confirmed, optimally-resected, stage III EOC who underwent surgical staging and had <1 cm residual disease [6].	Randomized to a 24-hour continuous intravenous infusion of 135 mg/m^2 paclitaxel on day 1 followed by an intravenous infusion of 75 mg/m^2 cisplatin (1 mg/min) on day 2 every 3 weeks for 6 cycles ***versus*** intravenous carboplatin (AUC 9.0) every 28 days for 2 cycles followed by a 24-hour continuous intravenous infusion of 135 mg/m^2 paclitaxel on day 1 and an intraperitoneal infusion of 100 mg/m^2 cisplatin on day 2 every 3 weeks for 6 cycles [6].	• Sequencing for *p53* mutations and IHC of p53 [8]. • Relative immunoblot expression of maspin to beta-actin [9]. • Methylation-specific PCR (MS-PCR) for the maspin promoter [9]; {Secord et al., in progress}. • IHC expression of maspin {Secord et al., in proqress}. • Relative immunoblot expression ofthrombospondin-1, bFGF, VEGF-A andVEGFR-1 to beta-actin [11]. • Methylation-specific PCR (MS-PCR) for the thrmobospondin-1 promoter [9]; {Secord et al., in progress}. • Microvessel density (MVD) hotspots for CD31 and CD105 [12]. • Relative immunoblot expression of Cyclin D1, cyclin E, cdk4, ki67, p16, Rb, p27 and p14, IHC expression of p16 and Rb, sequencing for p16 mutations and homozygous deletions [13]; {Havrilesky et al., in progress}. • Relative immunoblot expression of ΔNp63α to beta-actin [15]. • Relative immunoblot expression of XRCC3 to beta-actin {Panasci et al., in progress}.
GOG 132	Women with previously-untreated, histologically-confirmed, suboptimally-resected stage III and stage IV EOC who underwent surgical staging and had >1 cm residual disease [7]	Randomized to 100 mg/m^2 intravenous cisplatin (1 mg/minute) every 3 weeks for 6 cycles ***versus*** 200 mg/m^2 intravenous paclitaxel as a continuous 24 hour infusion every 3 weeks for 6 cycles ***versus*** 135 mg/m^2 intravenous paclitaxel as a continuous 24 hour infusion followed by 100 mg/m^2 intravenous cisplatin every 3 weeks for 6 cycles [7].	
GOG 157	Women with previously untreated, histologically-confirmed, completely-resected stage IA grade 3 (or clear cell tumors), stage IB grade 3 (or clear cell tumors), stage IC or stage II EOC who underwent optimal surgical staging [17].	Randomized to a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel and a 30-minute intravenous infusion of carboplatin (AUC7.5) every 3 weeks for 3 ***versus*** 6 cycles [17].	• IHC expression of p53 [3]. • IHC expression of p27 [18]; {Farley et al., in progress}. • IHC expression of cyclin E [18]; {Farley et al., in progress}. • IHC expression of thombospondin-1, angiopoietin-1, SPARC, VEGFR-2 (Flk-1), TIE-2 and VEGF-A [19]; {Garg et al., in progress}
GOG 158	Women with previously-untreated, histologically-confirmed, optimal-resected stage III EOC who underwent adequate	Randomized to a 24-hour intravenous infusion of 135 mg/m^2 paclitaxel on day 1 and 75 mg/m^2 intravenous cisplatin (1 mg/min) on day 2 every 3 weeks for 6 cycles	• Platinum-DNA adduct level by atomic absorption spectroscopy and transcript expression of the excision repair cross complementation group 1 (*ERCC1*) gene by

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	surgical staging and had <10 cm residual disease [20].	***versus*** a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1 and intravenous carboplatin (AUC 7.5 mg/ml/min) on day 1 every 3 weeks for 6 cycles 20].	reverse transcription-polymerase chain reaction (RT-PCR) [21].
GOG 175	Women with previously-untreated, histologically-confirmed, completely-resected stage IA grade 3 (or clear cell), stage IB grade 3 (or clear cell), stage IC or stage II EOC who underwent optimal surgical staging	Randomized to a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel and a 30-minute intravenous infusion of carboplatin (AUC 6) every 3 weeks for 3 cycles followed by a 1-hour intravenous infusion of 40 mg/m^2 every week for 24 weeks ***versus*** observation for 24 weeks {Mannel et al., in progress}.	• IHC expression of angiogenic markers and concentration of angiogenic markers in serum, plasma and urine {Kohn et al., in progress}. • Test of the virtual tissue banking mechnaism by examining IHC expression of Fanconi anemia complementation group (FANC), RAD51 and p53 families, and performing array-based comparative genomic hybridization (aCGH) analysis [22,23]; {Pejovic et al., in progress}.
GOG 172	Women with previously-untreated, histologically-confirmed, optimally-resected, stage III EOC who underwent adequate surgical staging and had <1 cm residual disease [24].	Randomized to a 24-hour continuous intravenous infusion of 135 mg/m^2 paclitaxel on day 1 followed by 75 mg/m^2 intravenous cisplatin on day 2 every 3 weeks for 6 cycles ***versus*** a 24-hour continuous intravenous infusion of 135 mg/m^2 paclitaxel on day 1 followed by 100 mg/m^2 intraperitoneal cisplatin on day 2 and 60 mg/m^2 intraperitoneal paclitaxel on day 8 every 3 weeks for 6 cycles [24].	• Sequencing for mutations and alterations in BRCA1 [26]; {Lesnock et al., in progress}. • MS-PCR for the *BRCA1* promoter and transcript expression of *BRCA1* by RT-PCR [27]. • IHC expression of BRCA1 [28], {Lesnock et al., in progress}. • *CHEK2* (CHK2) gene analysis by denaturing high-performance liquid chromatography, sequence analysis and single nucleotide polymorphism (SNP) genotyping by pyrosequencing [29]. • SNP genotyping of codon 118 and C8092A in ERCC1 by pyrosequencing [30,31] {Krivak et al., in progress}. • IHC expression of ERCC1 {Rubatt et al., in proqress}. • SNP genotyping of *BRCA1*, *BRCA2*, *ABCB1*, *ABCC2*, *ABCG2*, *XRCC1* and *GSTp1* using the Sequonom iPLEXTMGOLD Assay and MALDI-TOF platform [32,33] {Tian et al., in proqress}. • Genome wide SNP association analysis [Birreret al., in progress; Moore et al., in progress].
GOG 182	Women with previously-untreated, histologically-confirmed stage III or stage IV EOC or PPC with either optimally-resected disease (≤1 cm residual disease) or suboptimally-resected disease (>1 cm residual disease) following initial surgery [25].	Randomized to 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1 followed by intravenous carboplatin (AUC 6) on day 1 every 3 weeks for 8 cycles ***versus*** two triplets and two sequential doublets [24].*	
GOG 198	Women with women with histologically-confirimed FIGO stage III or IV epithelial ovarian, Fallopian tube or primary peritoneal cancer who were clinically and radiologically without evidence of disease but experienced biochemical recurrence as defined as a rising CA 125 that rose to exceed twice the upper-limit of normal limits.	Randomized to thalidomide 200 mg oral daily dose with weekly escalation of 100 mg to a maximum 400 mg ***versus*** tamoxifen 20 mg oral twice daily for up to 12-months {Hurteau et al., in progress}.	• Enzyme-linked immunosorbent assay (ELISA) for VEGF-A in pre-cycle 1 and off-treatment serum {Hurteau et al., in progress}. • ELISA for VEGF-A in up to 7 serial specimens alone and in combination with CA125 {Benbrook et al., in progress}. • BioRad multiplex luminex assays for angiogenic markers and cytokines in serial serum specimens {Benbrook et al., in progress}.
GOG 218	Women with previously-untreated epithelial ovarian, primary peritoneal or Fallopian tube cancer who underwent adequate surgical staging and cytoreduction with FIGO stage III disease with any gross or palpable residual	Randomized to a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel and intravenous carboplatin (AUC 6) over 30 minutes on day 1 every 3 weeks for 6 cycles plus placebo (for bevacizumab) on day 1 every 3 weeks from cycles 2 through 5	• Genomic profiles associated with platinum-resistance, PFS and OS {Michael Birrer}. • Angiogenic markers in tumor and serum with potential prognostic relevance based on GOG 170D{John Fruehauf}.

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	disease or FIGO stage IV disease.	followed by placebo (for bevacizumab) on day 1 from cycle 7 through 22 ***versus*** a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel and intravenous carboplatin (AUC 6) over 30 minutes on day 1 every 3 weeks for 6 cycles plus an intravenous infusion of 15 mg/kg bevacizumab on day 1 every 3 weeks from cycles 2 through 5 followed by placebo (for bevacizumab) on day 1 from cycle 7 through 22 ***versus*** a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel and intravenous carboplatin (AUC 6) over 30 minutes on day 1 every 3 weeks for 6 cycles plus an intravenous infusion of 15 mg/kg bevacizumab on day 1 every 3 weeks from cycles 2 through 5 followed by an intravenous infusion of 15 mg/kg bevacizumab on day 1 from cycle 7 through 22 {Burger et al., in progress}.	• SNPs in WNK1, GRK4 and KLKB1 associated with bevacizumab-induced hypertension {Doug Levine}. • Polymorphisms in codon 118 and C8092A in ERCC1 based on GOG 182 {Tom Krivak}. • Cell-free DNA in plasma {Anil Sood}. • EGFR/Her/ErbB family and ligands including soluble EGFR {Nita Maihle, Nicole Urban, Meenakshi Singh, Andre Baron}. • SNPs with potential predictive and prognostic clinical value {Tom Krivak, Kathleen Moore, Michael Birrer}.

* The experimental regimens included a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1, intravenous 800 mg/m^2/day gemcitabine on day 1 and day 8 and intravenous carboplatin (AUC 5) on day 1 every 3 weeks for 8 cycles ***versus*** a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1, 30 mg/m^2 intravenous methoxylpolyethylene glycosylated (polyethylene glycol [PEG])-liposomal doxorubicin every other day 1 and intravenous carboplatin (AUC 5) on day 1 every 3 weeks for 8 cycles ***versus*** 1.25 mg/m^2/day intravenous topotecan on day 1 and day 3 and intravenous carboplatin (AUC 5) on day 3 every 3 weeks for 4 cycles followed by a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1 and intravenous carboplatin (AUC 6) on day 1 every 3 weeks for 4 cycles ***versus*** 1000 mg/m^2/day intravenous gemcitabine on day 1 and day 8 followed by intravenous carboplatin (AUC 6) on day 8 every 3 weeks for 4 cycles followed by a 3-hour intravenous infusion of 175 mg/m^2 paclitaxel on day 1 and intravenous carboplatin (AUC 6) on day 1 every 3 weeks for 4 cycles [25].