## Supplementary appendix

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A randomized trial of five years of letrozole versus placebo after aromatase inhibitor-based therapy: NRG Oncology/NSABP B-42.

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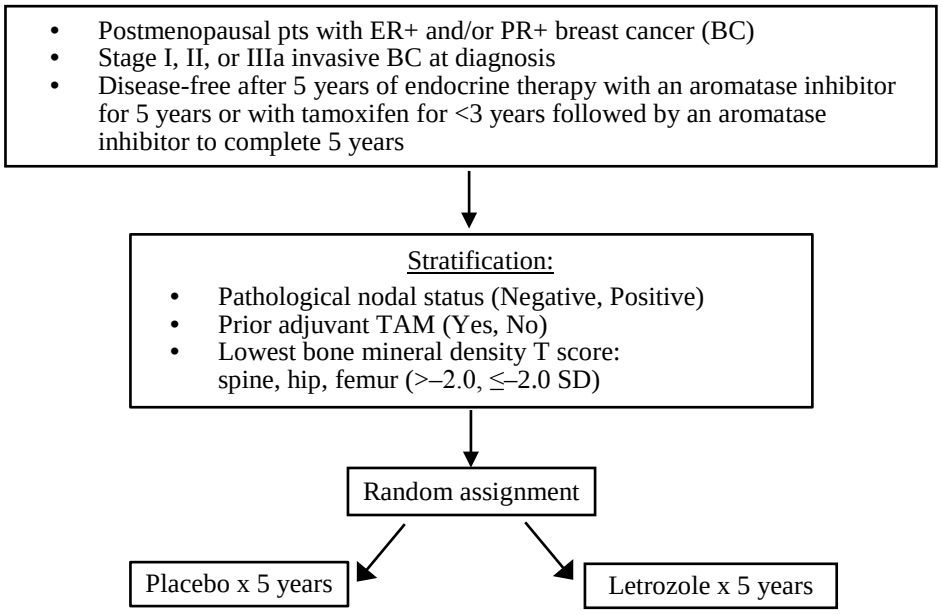
**Appendix Figure 1: NRG Oncology/NSABP B-42 schema**



**Appendix Table 1: Recruitment by active sites**

**NSABP B-42**

| Institution | Principal Investigator | Accrual |
|---|---|---|
| Cancer Trials Support Unit | Stephen E Riordan | 897 |
| Kaiser Permanente-Vallejo | Louis Fehrenbacher | 149 |
| CCOP Southeast Cancer Control Consortium | James N Atkins | 140 |
| BCCA-Vancouver Cancer Centre | Lorna M Weir | 105 |
| University of Pittsburgh | Adam Brufsky | 83 |
| Ireland Cooperative Oncology Research Group | Brian Moulton | 80 |
| CCOP Missouri Valley Cancer Consortium | Gamini Soori | 70 |
| CCOP Atlanta Regional | Thomas E Seay | 63 |
| CCOP Wichita | Shaker R Dakhil | 63 |
| CCOP Central Illinois | James L Wade | 61 |
| MedStar Franklin Square Medical Center/Weinberg Cancer Institute | John L Zapas | 57 |
| Florida Cancer Specialists - Sarasota Downtown | Fadi Kayali | 53 |
| CCOP Michigan Cancer Research Consortium CCOP | Philip J Stella | 52 |
| Hartford Hospital | Patricia A DeFusco | 51 |
| CCOP Christiana Care Health System-Christiana Hospital | David D Biggs | 50 |
| CCOP Northern Indiana Cancer Research Consortium | Bilal Ansari | 48 |
| Michigan State University Clinical Center | Deimante M Tamkus | 47 |
| Aurora Cancer Care - Milwaukee West | Rubina Qamar | 44 |
| CCOP Colorado Cancer Research Program | Keren Sturtz | 43 |
| CHUM-Hôtel Dieu du Montréal | André Robidoux | 40 |
| Puget Sound Oncology Consortium - Fred Hutchinson Cancer Research Center | Tanya A Wahl | 39 |
| CCOP Evanston-NorthShore University HealthSystem | Douglas E Merkel | 37 |
| Thompson Cancer Survival Center | Daniel M Ibach | 36 |
| Kaiser Permanente - San Diego Mission | Jonathan A Polikoff | 34 |
| West Virginia University | Mohamad A Salkeni | 33 |
| CCOP Metro-Minnesota | Richard T Zera | 33 |
| Ohio State University Medical Center | William B Farrar | 31 |
| CCOP Columbus | John P Kuebler | 29 |
| Aultman Health Foundation - Aultman Hospital Foundation | Shruti Trehan | 28 |
| Rutgers Cancer Institute of NJ-Robert Wood Johnson University Hospital | Deborah L Toppmeyer | 25 |
| CCOP Heartland Cancer Research | Bryan A Faller | 25 |
| Cancer Centre of Southeastern Ontario at Kingston General Hospital | Conrad B Falkson | 25 |
| Greater Baltimore Medical Center | Madhu Chaudhry | 25 |
| Mount Sinai Medical Center | Michael A Schwartz | 25 |
| CCOP Hematology Oncology Associates of CNY PC - East Syracuse | Jeffrey J Kirshner | 25 |
| University of Iowa Hospitals and Clinics | Mark W Karwal | 24 |
| Scripps Cancer Center | James R Mason | 24 |
| UF Cancer Center at Orlando Health | Eleftherios P Mamounas | 24 |
| Thomas Jefferson University Hospital | Scott D Goldstein | 24 |
| North Shore University Hospital CCOP | Lora R Weiselberg | 24 |
| University of California at San Diego | Anne M Wallace | 23 |
| Advocate Lutheran General Hospital | Jacob D Bitran | 23 |
| M D Anderson Cancer Center | Henry M Kuerer | 22 |
| CCOP William Beaumont Hospital - Royal Oak | John M Robertson | 22 |
| CCOP Ochsner Clinic - CCOP Ochsner Medical Center Jefferson | Marc R Matrana | 22 |

| | | |
|---|---|---|
| CCOP Sanford Medical Center – Fargo | Preston D Steen | 22 |
| Cancer Care Manitoba, Manitoba | Debjani Grenier | 21 |
| New York Oncology Hematology PC – Albany | John T Phelan | 21 |
| Allegheny Cancer Center at Allegheny General Hospital | Thomas B Julian | 21 |
| CCOP Dayton | Howard M Gross | 21 |
| CCOP Greenville Health System Cancer Institute | Jeffrey K Giguere | 21 |
| City of Hope | Lily L Lai | 20 |
| Le Centre hospitalier affilié universitaire de Québec - Saint-Sacrement | Louise Provencher | 20 |
| LDS Hospital, Provo | Robert D Noyes | 20 |
| CCOP Western Oncology Research Consortium | Alison K Conlin | 20 |
| CCOP St Vincent Hospital | Matthew L Ryan | 19 |
| University Health Network-Princess Margaret Hospital | David R McCready | 19 |
| Saint Mary Medical Center - Pacific Shores Medical Group | Nerses S Tchekmedyian | 18 |
| CCOP Northwest | John A Keech | 18 |
| CCOP Upstate Carolina | James D Bearden | 17 |
| Saint Mary's Hospital | Jaroslav F Prchal | 16 |
| West Virginia University Charleston | Steven J Jubelirer | 16 |
| Alamance Regional Medical Center | Janak K Choksi | 16 |
| Oncology and Hematology Care Inc - Blue Ash | Patrick J Ward | 16 |
| CCOP Ozark Health Ventures LLC-Cancer Research for The Ozarks Springfield | Jay W Carlson | 16 |
| Norton Health Care Pavilion – Downtown | John T Hamm | 15 |
| University of Hawaii Cancer Center | Kenneth NM Sumida | 15 |
| CCOP Mainline Health | Thomas G Frazier | 15 |
| York Hospital | L Eamonn Boyle | 15 |
| Baton Rouge General Medical Center | Andrew D Lauve | 15 |
| Edna Williams Cancer Center at the Baptist Cancer Institute | Troy H Guthrie | 14 |
| MBCCOP University of New Mexico | Mohammad H Fekrazad | 14 |
| Credit Valley Hospital, Mississauga, Ontario | Robert E Myers | 14 |
| Henry Ford Hospital | Thomas J Doyle | 14 |
| Thunder Bay Regional Health Sciences Centre | Margaret L Anthes | 14 |
| CCOP Montana Cancer Consortium | Benjamin T Marchello | 14 |
| Royal Victoria Hospital | Henry R Shibata | 13 |
| Wake Forest University Health Sciences | Edward A Levine | 13 |
| University of Miami Miller School of Medicine-Sylvester Cancer Center | Frederick L Moffat | 13 |
| Desert Regional Medical Center, Palm Springs | Elber S Camacho | 13 |
| Edward Hospital/Cancer Center, Naperville | Alexander Hantel | 13 |
| CCOP Marshfield Clinic | Jessica A Wernberg | 13 |
| Newark Beth Israel Medical Center, Newark | Lori Schleicher | 12 |
| Eastern Maine Medical Center, Bangor | Thomas H Openshaw | 12 |
| Georgia Regents University Medical Center | Anand Jillella | 12 |
| Baylor College of Medicine | Mothaffar F Rimawi | 12 |
| CCOP Grand Rapids Clinical Oncology Program | Kathleen J Yost | 12 |
| CCOP Illinois Oncology Research Association | Nguyet A Le-Lindqwister | 12 |
| Hennepin County Medical Center | Richard T Zera | 11 |
| University of Colorado | Nicole Kounalakis | 11 |
| Cancer Institute at Alexian Brothers | Kevin P McKian | 11 |
| CCOP Virginia Mason | Craig R Nichols | 11 |
| Essentia Health Cancer Center - South University Clinic, Fargo | Mahendra K Gupta | 11 |
| Akron City Hospital | Jennifer E Payne | 10 |
| Emory University/Winship Cancer Institute | Toncred M Styblo | 10 |

| | | |
|---|---|---|
| University of Vermont | Seth P Harlow | 9 |
| Jewish General Hospital | Richard G Margolese | 9 |
| Albert Einstein Medical Center | Mark S Morginstin | 9 |
| Sutter General Hospital | Stacy D D'Andre | 9 |
| Virginia Commonwealth University | Harry D Bear | 9 |
| CCOP Natalie W Bryant Cancer Center | James B Lockhart | 9 |
| CCOP Sanford Research USD | Miroslaw A Mazurczak | 9 |
| Lehigh Valley Hospital, Allentown | Lori C Alfonse | 8 |
| MBCCOP Boston Medical Center | Maureen T Kavanah | 8 |
| Sutter Cancer Research Consortium | Ari D Baron | 8 |
| University of Kentucky | Edward H Romond | 8 |
| Health Sciences North | Scott Young | 8 |
| Oncology and Hematology Associates of Southwest Virginia, Roanoke | Paul D Richards | 8 |
| Staten Island University Hospital, Staten Island | Terenig Terjanian | 8 |
| Covenant Medical Center-Lakeside | Ibrahim A Shalaby | 8 |
| Regional Hospital of Scranton | Martin Hyzinski | 8 |
| Berkshire Hematology Oncology, P.C. | Harvey Zimbler | 7 |
| Stanford University Hospitals and Clinics | Irene L Wapnir | 7 |
| UC Irvine Medical Ctr/Chao Family Comprehensive Cancer Ctr | Rita S Mehta | 7 |
| Case Western Reserve University | Robert Shenk | 7 |
| Western Pennsylvania Hospital | John A Lech | 7 |
| CCOP Kalamazoo Center for Medical Studies | Raymond S Lord | 7 |
| CCOP Carle Foundation - Carle Cancer Center | Kendrith M Rowland | 7 |
| CCOP Toledo Community Hospital Oncology Program | Rex B Mowat | 7 |
| University of Missouri - Ellis Fischel | Clint D Kingsley | 6 |
| Froedtert and the Medical College of Wisconsin | Alonzo P Walker | 6 |
| MBCCOP Gulf Coast | Thaddeus A Beeker | 6 |
| Morton Plant Hospital | Hitesh Patel | 6 |
| The Community Hospital | Erwin L Robin | 6 |
| Kootenai Cancer Center, Post Falls | Kevin T Kim | 6 |
| CCOP Geisinger Medical Center | Victor G Vogel | 5 |
| University of Connecticut | Bruce M Brenner | 5 |
| East Carolina University | Darla K Liles | 5 |
| Providence Hospital, Southfield | Anibal Drelichman | 5 |
| Phoebe Putney Memorial Hospital | Jose M Tongol | 5 |
| CCOP St Louis-Cape Girardeau | Bethany G Sleckman | 5 |
| CCOP Iowa Oncology Research Association | Robert J Behrens | 5 |
| South Pointe Hospital | John H Suh | 4 |
| Clearview Cancer Institute | Jeremy K Hon | 4 |
| Baptist Health Louisville | Udaya G Joseph | 4 |
| Metairie Oncologists | Jayne Gurtler | 4 |
| CCOP Essentia Health Duluth Clinic | Daniel A Nikcevich | 4 |
| Bay Area Tumor Institute | Tom K Lee | 4 |
| Aurora Sinai Medical Center | Magdalena Flejsierowicz | 4 |
| University of Texas Health Science Center | Ismail Jatoi | 3 |
| Saint Louis University Hospital | Paul J Petruska | 3 |
| Odette Cancer Centre- Sunnybrook Health Sciences Centre | Jean-Philippe Pignol | 3 |
| Nebraska Methodist Hospital | James A Reilly | 3 |
| Medical University of South Carolina, Charleston | Eric T Kimchi | 3 |
| University of Arkansas for Medical Sciences, Little Rock | V Suzanne Klimberg | 2 |

| | | |
|---|---|---|
| Lahey Hospital and Medical Center | Stephen E Karp | 2 |
| Montréal General Hospital | Michael P Thirlwell | 2 |
| University of California at Los Angeles (UCLA) | Patricia A Ganz | 2 |
| University of Florida | Carmen Allegra | 2 |
| Baystate Medical Center, Springfield | Grace Makari-Judson | 2 |
| Glens Falls Hospital | Robert W Sponzo | 2 |
| Rush University Medical Center | Melody A Cobleigh | 1 |
| Saint Vincent Hospital and Health Services | Ruemu E Birhiray | 1 |
| Saint Joseph Hospital | Lawrence D Wagman | 1 |
| Stony Brook University Medical Center | Andrzej P Kudelka | 1 |
| MBCCOP John H Stroger Jr Hospital of Cook County | Thomas E Lad | 1 |
| CCOP Kansas City | Rakesh Gaur | 1 |
| Santa Rosa Memorial Hospital | Ian C Anderson | 1 |

**Appendix Table 2: Distribution of causes of death by treatment group: NRG Oncology/NSABP B-42**

| Cause of death | Treatment | | |
|---|---|---|---|
| | Placebo (n=146) | Letrozole (n=164) | Total (n=310) |
| Breast cancer | 47 | 46 | 93 |
| Second primary non-breast malignancy | 36 | 38 | 74 |
| **CNS disease** | | | |
| Hemorrhage | 4 | 4 | 8 |
| Other | 3 | 4 | 7 |
| **Cardiovascular disease** | | | |
| Ischemic | 6 | 5 | 11 |
| Heart failure | 4 | 6 | 10 |
| Arrhythmia | 1 | 2 | 3 |
| Renal disease | 1 | 1 | 2 |
| Pulmonary disease | 7 | 8 | 15 |
| Gastrointestinal, liver disease | 6 | 1 | 7 |
| Infection | 6 | 2 | 8 |
| Accidental death, suicide | 0 | 2 | 2 |
| Adverse events, not otherwise classified | 1 | 4 | 5 |
| Cause unknown | 24 | 41 | 65 |

**Appendix Table 3: Distributions of sites of distant recurrence by treatment group: NRG Oncology/NSABP B-42**

| Location of distant recurrence | Treatment | | |
|---|---|---|---|
| | Placebo (n=102) | Letrozole (n=73) | Total (n=175) |
| Bone | 20 | 14 | 34 |
| Lung/pleura/mediastinum | 13 | 4 | 17 |
| Liver | 5 | 7 | 12 |
| Soft tissue, lymph nodes | 3 | 2 | 5 |
| Abdomen | 3 | 0 | 3 |
| Brain | 1 | 2 | 3 |
| Other, non-specified | 1 | 0 | 1 |
| Multiple sites of recurrence | 56 | 44 | 100 |

**Appendix Table 4: Adverse events reported on NSABP B-42[*†]**

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Overall | 219 ( 11.3 %) | 418 ( 21.6 %) | 53 ( 2.7 %) | 26 ( 1.3 %) | 263 ( 13.5 %) | 486 ( 25 %) | 51 ( 2.6 %) | 25 ( 1.3 %) |
| Arthralgia | 253 ( 13.1 %) | 47 ( 2.4 %) | 0 ( 0 %) | 0 ( 0 %) | 296 ( 15.2 %) | 50 ( 2.6 %) | 0 ( 0 %) | 0 ( 0 %) |
| Myalgia | 99 ( 5.1 %) | 19 ( 1 %) | 0 ( 0 %) | 0 ( 0 %) | 133 ( 6.9 %) | 16 ( 0.8 %) | 0 ( 0 %) | 0 ( 0 %) |
| Back pain | 0 ( 0 %) | 44 ( 2.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 38 ( 2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Fracture | 0 ( 0 %) | 29 ( 1.5 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 36 ( 1.9 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Cholesterol high | 27 ( 1.4 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 30 ( 1.5 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypertension | 0 ( 0 %) | 27 ( 1.4 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 27 ( 1.4 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Dyspnea | 0 ( 0 %) | 22 ( 1.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 29 ( 1.5 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Thromboembolic event | 15 ( 0.8 %) | 9 ( 0.5 %) | 8 ( 0.4 %) | 0 ( 0 %) | 11 ( 0.6 %) | 9 ( 0.5 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Hypertriglyceridemia | 25 ( 1.3 %) | 5 ( 0.3 %) | 1 ( 0.1 %) | 0 ( 0 %) | 20 ( 1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hot flashes | 0 ( 0 %) | 16 ( 0.8 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 28 ( 1.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cataract | 0 ( 0 %) | 20 ( 1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 21 ( 1.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urinary tract infection | 0 ( 0 %) | 17 ( 0.9 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 18 ( 0.9 %) | 4 ( 0.2 %) | 0 ( 0 %) |
| Atrial fibrillation | 0 ( 0 %) | 16 ( 0.8 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 20 ( 1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Fatigue | 0 ( 0 %) | 17 ( 0.9 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 20 ( 1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Syncope | 0 ( 0 %) | 16 ( 0.8 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 21 ( 1.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Anemia | 0 ( 0 %) | 11 ( 0.6 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 17 ( 0.9 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Lung infection | 0 ( 0 %) | 13 ( 0.7 %) | 2 ( 0.1 %) | 4 ( 0.2 %) | 0 ( 0 %) | 14 ( 0.7 %) | 0 ( 0 %) | 0 ( 0 %) |
| Acute coronary syndrome | 4 ( 0.2 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 12 ( 0.6 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Myocardial infarction | 0 ( 0 %) | 11 ( 0.6 %) | 2 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) | 11 ( 0.6 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Dizziness | 0 ( 0 %) | 15 ( 0.8 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 11 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) |
| Diarrhea | 0 ( 0 %) | 16 ( 0.8 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 9 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) |
| Heart failure | 0 ( 0 %) | 6 ( 0.3 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 14 ( 0.7 %) | 2 ( 0.1 %) | 1 ( 0.1 %) |
| Pain | 0 ( 0 %) | 11 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 14 ( 0.7 %) | 0 ( 0 %) | 0 ( 0 %) |
| Depression | 0 ( 0 %) | 4 ( 0.2 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 12 ( 0.6 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Hyperglycemia | 0 ( 0 %) | 8 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 14 ( 0.7 %) | 2 ( 0.1 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Skin infection | 0 ( 0 %) | 12 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 11 ( 0.6 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Headache | 0 ( 0 %) | 11 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 12 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) |
| Abdominal pain | 0 ( 0 %) | 9 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 13 ( 0.7 %) | 0 ( 0 %) | 0 ( 0 %) |
| Left ventricular systolic dysfunction | 0 ( 0 %) | 5 ( 0.3 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 10 ( 0.5 %) | 4 ( 0.2 %) | 1 ( 0.1 %) |
| Infections and infestations - Other, specify | 0 ( 0 %) | 15 ( 0.8 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Surgical and medical procedures - Other, specify | 0 ( 0 %) | 11 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 10 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hyponatremia | 0 ( 0 %) | 11 ( 0.6 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 6 ( 0.3 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Stroke | 5 ( 0.3 %) | 2 ( 0.1 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 5 ( 0.3 %) | 4 ( 0.2 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Cardiac disorders - Other, specify | 0 ( 0 %) | 8 ( 0.4 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Dehydration | 0 ( 0 %) | 10 ( 0.5 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Insomnia | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 10 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 7 ( 0.4 %) | 1 ( 0.1 %) | 3 ( 0.2 %) |
| Musculoskeletal and connective tissue disorder - Other, specify | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 10 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) |
| Nausea | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 9 ( 0.5 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vomiting | 0 ( 0 %) | 11 ( 0.6 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cholecystitis | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 8 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypokalemia | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 4 ( 0.2 %) | 0 ( 0 %) |
| Small intestinal obstruction | 0 ( 0 %) | 7 ( 0.4 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Colitis | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gastrointestinal disorders - Other, specify | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 8 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Respiratory failure | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 4 ( 0.2 %) |
| Aspartate aminotransferase increased (AST/SGOT) | 0 ( 0 %) | 4 ( 0.2 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Fall | 0 ( 0 %) | 8 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Arthritis | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Nervous system disorders - Other, specify | 0 ( 0 %) | 3 ( 0.2 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Pain in extremity | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Renal calculi | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Wound infection | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Acute kidney injury | 0 ( 0 %) | 4 ( 0.2 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Cardiac troponin I increased | 1 ( 0.1 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Aortic valve disease | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 2 ( 0.1 %) | 1 ( 0.1 %) |
| Alanine aminotransferase increased (ALT/SGPT) | 0 ( 0 %) | 3 ( 0.2 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Appendicitis | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Intracranial hemorrhage | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 3 ( 0.2 %) |
| Osteoporosis | 0 ( 0 %) | 6 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vaginal dryness | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 7 ( 0.4 %) | 0 ( 0 %) | 0 ( 0 %) |
| Respiratory, thoracic and mediastinal disorders - Other, specify | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Edema limbs | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Anorexia | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cardiac arrest | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 1 ( 0.1 %) |
| Hypoxia | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vaginal hemorrhage | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Wrist fracture | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bronchial infection | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urinary tract obstruction | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Non-cardiac chest pain | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Anaphylaxis | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Chest pain - cardiac | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hip fracture | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypercalcemia | 0 ( 0 %) | 1 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Hyperkalemia | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Hypotension | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Injury, poisoning and procedural complications - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Pleural effusion | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Rectal hemorrhage | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Sepsis | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 1 ( 0.1 %) |
| Vascular disorders - Other, specify | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Weight loss | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 5 ( 0.3 %) | 0 ( 0 %) | 0 ( 0 %) |
| Joint range of motion decreased | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bone pain | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cardiac troponin T increased | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Constipation | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Encephalopathy | 0 ( 0 %) | 4 ( 0.2 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hepatobiliary disorders - Other, specify | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Joint infection | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Lymphocyte count decreased | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Myelodysplastic syndrome | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) |
| Peripheral motor neuropathy | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Peripheral sensory neuropathy | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pulmonary edema | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Rash maculo-papular | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Sinus bradycardia | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Visceral arterial ischemia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Upper gastrointestinal hemorrhage | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Enterocolitis infectious | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Dyspepsia | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Eye disorders - Other, specify | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hearing impaired | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hematoma | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) |
| Memory impairment | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Neuralgia | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Neutrophil count decreased | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Pancreatitis | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 4 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Platelet count decreased | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Renal and urinary disorders - Other, specify | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urinary incontinence | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Leukemia secondary to oncology chemotherapy | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 2 ( 0.1 %) |
| Generalized muscle weakness | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Aortic injury | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Appendicitis perforated | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Aspiration | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Atrial flutter | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Atrioventricular block complete | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bladder infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Blood bilirubin increased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Chest wall pain | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Creatinine increased | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Depressed level of consciousness | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Dysphagia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Enterocolitis | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| General disorders and administration site conditions - Other, specify | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypoglycemia | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypophosphatemia | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) |
| Neck pain | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pericardial effusion | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Peripheral ischemia | 0 ( 0 %) | 3 ( 0.2 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pneumonitis | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Psychosis | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Skin and subcutaneous tissue disorders - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Skin ulceration | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Supraventricular tachycardia | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Venous injury | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ventricular tachycardia | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Treatment related secondary malignancy | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Abdominal infection | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Soft tissue infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Muscle weakness upper limb | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Agitation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Anxiety | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ataxia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Breast infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cerebrospinal fluid leakage | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cognitive disturbance | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Colonic hemorrhage | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Death NOS | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Flu like symptoms | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gallbladder pain | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gastritis | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Glaucoma | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hematuria | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hyperuricemia | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Hypomagnesemia | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ileus | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Kidney infection | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Lipase increased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Multi-organ failure | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pelvic pain | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pruritus | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Renal colic | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Reproductive system and breast disorders - Other, specify | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Restrictive cardiomyopathy | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Seizure | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Sick sinus syndrome | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Sleep apnea | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Small intestinal perforation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Spinal fracture | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Suicide attempt | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) |
| Vaginal inflammation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vasovagal reaction | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Weight gain | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Lower gastrointestinal hemorrhage | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| GGT increased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Right ventricular dysfunction | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bone infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Eyelid function disorder | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Tricuspid valve disease | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pelvic floor muscle weakness | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Chronic kidney disease | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Muscle weakness lower limb | 0 ( 0 %) | 2 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Soft tissue necrosis lower limb | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Abdominal distension | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Adult respiratory distress syndrome | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Alkaline phosphatase increased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Amnesia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ankle fracture | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Blood and lymphatic system disorders - Other, specify | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Blurred vision | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Breast pain | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bronchospasm | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Catheter related infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Colonic fistula | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Colonic perforation | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Colonic stenosis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Conduction disorder | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Confusion | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cough | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Delirium | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Duodenal perforation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Duodenal ulcer | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Dyspareunia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Endocrine disorders - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Epistaxis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Extrapyramidal disorder | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gait disturbance | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gallbladder obstruction | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gastric hemorrhage | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gastric perforation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hemorrhoids | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hepatic failure | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Hepatic pain | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hoarseness | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypermagnesemia | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypernatremia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hyperthyroidism | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Hypocalcemia | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Hypothyroidism | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Injury to carotid artery | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Investigations - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Irregular menstruation | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Joint effusion | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Kyphosis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Lymphedema | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Meningitis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Menorrhagia | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Metabolism and nutrition disorders - Other, specify | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Mobitz (type) II atrioventricular block | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Mobitz type I | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Myelitis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Otitis media | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Personality change | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Pharyngitis | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pleuritic pain | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pulmonary hypertension | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Rash acneiform | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Retinopathy | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Seroma | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Serum amylase increased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Stomach pain | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Stridor | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Suicidal ideation | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Superior vena cava syndrome | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Thrombotic thrombocytopenic purpura | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Tinnitus | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Tracheal obstruction | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Tremor | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urinary retention | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urticaria | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Uterine hemorrhage | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vasculitis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ventricular fibrillation | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Vertigo | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| White blood cell decreased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Ejection fraction decreased | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bile duct stenosis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pancreas infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Glucose intolerance | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Abducens nerve disorder | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Duodenal hemorrhage | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Intra-abdominal hemorrhage | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Intraoperative hemorrhage | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Mediastinal hemorrhage | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) |
| Pelvic infection | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Edema trunk | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |

| | Placebo (n=1933) | | | | Letrozole (n=1941) | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Laryngeal obstruction | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Nail infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Optic nerve disorder | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pleural infection | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Mitral valve disease | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Anorectal infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Vascular access complication | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Sinus disorder | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Localized edema | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Cystitis noninfective | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Device related infection | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Urinary fistula | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Pancreatic duct stenosis | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Ileal obstruction | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Jejunal obstruction | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Peripheral nerve infection | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Bladder anastomotic leak | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Prolapse of urostomy | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |
| Avascular necrosis | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) |
| Gastroesophageal reflux disease | 0 ( 0 %) | 1 ( 0.1 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) | 0 ( 0 %) |

[*]Adverse events of grade 1 or 2 occurring in ≥10% of patients and all grade 3, 4, and 5 events are reported in the table. Per protocol, adverse events were to be reported every 6 months during study therapy, 6 months after the last administered dose, and beyond 6 months after the last administered dose if possibly, probably, or definitely attributed to the investigational agent.

[†]Only the following grade 2 adverse events (and grade 1 as noted in parentheses) had to be reported: acute coronary syndrome, cholesterol high, hypertriglyceridemia, arthralgia, myalgia, ischemia cerebrovascular, stroke (grade 1 and 2), transient ischemia attack (grade 1 and 2), peripheral ischemia, thromboembolic events, and visceral arterial ischemia.

NSABP B-42 PROTOCOL SUMMARY OF CHANGES

For Protocol Amendment #6 to: NSABP B-42

NCI Protocol #: NSABP B-42
Local Protocol #: NSABP B-42

NCI Version Date: December 7, 2010
Protocol Date: April 16, 2014

Protocol Title: A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer

*A list of changes from the previous CTEP approved version of the protocol is provided. Specific text additions and changes are highlighted and in* ***bold.***

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 1. | | | *The following changes have been made throughout the revised protocol:*<br>• *The NSABP and the NSABP Operations Center were changed to NRG Oncology, where appropriate.*<br>• *As part of the restructuring of the cooperative groups, the name of the NSABP Biostatistical Center has been changed to the NRG Oncology Statistics and Data Management Center (SDMC). All references to NSABP Biostatistical Center have been changed to NRG Oncology SDMC.*<br>• *Divisions are now referred to as Departments within NRG Oncology. Division has been changed to Department where appropriate.*<br>• *References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)."* | |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 2. | **NSABP PROTOCOL B-42** | 1 | NSABP PROTOCOL B-42<br>A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer<br>~~NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)~~ | **NRG ONCOLOGY**<br>NSABP PROTOCOL B-42<br>A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer<br>**This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: Alliance, ECOG-ACRIN, and SWOG**<br>*Effective 03/01/14, the NSABP became part of the NCTN group NRG Oncology.* |
| 3. | **NSABP PROTOCOL B-42** | 1 | ~~Four~~ Allegheny Center – ~~5th Floor~~<br>Pittsburgh, PA 15212~~-5234~~<br>TELEPHONE: 412-~~330-4600~~<br>~~FAX: 412-330-4660~~ | **Two** Allegheny Center – **Suite 1200**<br>Pittsburgh, PA 15212<br>TELEPHONE: 412-**339-5300**<br>*New address and phone number effective 01/20/14.* |
| 4. | **NSABP PROTOCOL B-42** | 1 | ~~All institutions that are not aligned with the NSABP will enroll patients via the NCI Cancer Trials Support Unit (CTSU).~~ | N/A |
| 5. | **NSABP PROTOCOL B-42** | 1 | Version Date: ~~December 7, 2010~~ (Replaces all other versions) | **NCI** Version Date: **April 16, 2014** (Replaces all other versions) |
| 6. | **Protocol Revision Record** | 4 | N/A | *The Protocol Revision Record has been updated to include the changes made in Amendment #6.* |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 7. | **Information Resources Row 2, Cols 2 and 3** | 9 | ~~Four~~ Allegheny Center – ~~5th Floor~~<br>Pittsburgh, PA 15212~~-5234~~ | **Two** Allegheny Center – **Suite 1200**<br>Pittsburgh, PA 15212 |
| | | | Phone: 412~~-330-4600~~<br>~~Fax: 412-330-4660~~ | Phone: 412-**339-5300** |
| 8. | **Information Resources Row 4, Col 3** | 9 | Phone: 412~~-330-4600~~<br>~~Fax: 412-330-4661~~ | Phone: 412-33**9-5300**<br>**E-mail: regulatory@nsabp.org** |
| 9. | **Information Resources Row 5, Col 3** | 9 | Phone: 1-8~~88-823-5923~~<br>Fax: 215-569-0206 | Phone: 1-8**66-651-2878**<br>Fax: 215-569-0206<br>**E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)** |
| 10 | **Information Resources Row 8, Col 2** | 9 | Pharmaceutical Management Branch<br>For mail:<br>CTEP, DCTD, NCI<br>~~9000 Rockville Pike~~<br>~~EPN, Room 7149~~<br>Bethesda, MD 20892~~-7422~~<br>For express courier:<br>CTEP, DCTD, NCI<br>~~6130 Executive Blvd.~~<br>~~Room 7149~~<br>Rockville, MD 2085~~2~~ | Pharmaceutical Management Branch<br>For mail **(USPS)**:<br>CTEP, DCTD<br>**NCI Shady Grove**<br>**Room 5W228, MSC 9725**<br>**9609 Medical Center Drive**<br>Bethesda, MD 20892-**9725**<br>For express courier:<br>**Pharmaceutical Management Branch,**<br>CTEP, DCTD,<br>NCI **Shady Grove**<br>**Room 5W228, MSC 9725**<br>**9609 Medical Center Drive**<br>Rockville, MD 2085**0**<br>*Updated to current PMB mailing addresses.* |
| 11 | **Information Resources Row 8, Col 3** | 9 | Phone: ~~301-496-5725~~<br>Fax: ~~301-480-4612~~ | Phone: **240-276-6575**<br>Fax: **240-276-7893**<br>**E-mail: PMBAfterHours@mail.nih.gov**<br>*Updated to current PMB phone and fax numbers, and e-mail address.* |
| 12 | **Information Resources Row 11, Col 3** | 9 | Phone: ~~412-359-3312~~ | Phone: **412-697-6611** |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 13 | **Cancer Trials Support Unit (CTSU) Information Resources**<br>**Row 2, Col 1** | 11 | Phone: 1-~~888-823-5923~~<br>Fax: 1-215-569-0206 | *Rationale: Change made to be consistent with updated NCTN CTSU information.*<br>Phone: 1-8**66-651-2878**<br>Fax: 1-215-569-0206<br>**E-mail: CTSURegulatory @ctsu.coccg.org (for submitting regulatory documents only)** |
| 14 | **Cancer Trials Support Unit (CTSU) Information Resources**<br>**Row 2, Col 3** | 11 | Submit study data directly to the ~~NSABP~~ unless otherwise specified in the protocol~~:~~ | Submit study data directly to the **NRG Oncology SDMC through the Online Data Entry function** unless otherwise specified in the protocol**.**<br>**Submit study data online through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account.** |
| 15 | **Cancer Trials Support Unit (CTSU) Information Resources**<br>**Row 6** | 11 | ~~The CTSU Public Web site is located at www.ctsu.org~~<br>The CTSU Registered Member Web site is located at https://~~members~~.ctsu.org | The CTSU Registered Member Web site is located at https://www.ctsu.org |
| 16 | **Cancer Trials Support Unit (CTSU) Information Resources**<br>**Row 7, Bullet 1** | 11 | The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://~~members~~.ctsu.org. | The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. |
| 17 | **9.1.5**<br>**9.1.7**<br>**9.1.8**<br>**9.1.9** | 34<br>36<br>36<br>36 | PMB phone number updated from 301-496-5725 to **240-276-6575**.<br>PMB fax number updated from 301-402-0429 to **240-276-7893**. | |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 18 | **10.3**<br>**Paragraph 2** | 38 | An ~~AdEERS~~ report must be submitted to the ~~NSABP~~ Lead Group using the electronic web-based application located at ~~https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup~~. When initiating ~~an AdEERS~~ report, the reporter will be directed to refer to the protocol for expedited reporting requirements. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to ~~the NCI~~ by telephone at: ~~301-897-7497~~. | A **CTEP-AERS** report must be submitted to the **NRG Oncology** Lead Group using the electronic web-based application located at **https://eapps-ctep.nci.nih.gov/ctepaers**. When initiating **a CTEP-AERS** report, the reporter will be directed to refer to the protocol for expedited reporting requirements. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to **NRG Oncology** by telephone at: **412-624-2666**. |
| 19 | **10.4**<br>**10.4.1** | 41<br>41 | *The instructions for reporting secondary malignancies in Section 10.4 and second malignancies in Section 10.4.1 were revised to be consistent with the instructions provided in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements" (dated September 16, 2013).* | |
| 20 | **10.5** | 41 | *Pregnancy reporting updated to the definitions and reporting instruction in the Cancer Therapy Evaluation Program's revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6). See the revised protocol for complete text.* | |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 21 | **Appendix B 4.0 Paragraphs 1-2** | 74 | All case report forms (CRFs) associated with this study must be downloaded from the NSABP B-42 Web page located on the CTSU Registered members site (https://~~members~~.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.<br><br>Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the ~~NSABP Biostatistical Center~~. ~~The preferred method of sending data is via fax at~~ 412-622-2111. ~~Do not include a cover sheet for faxed data.~~ | All case report forms (CRFs) associated with this study must be downloaded from the NSABP B-42 Web page located on the CTSU Registered members site (https://www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.<br><br>Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the **NRG Oncology SDMC**. **Submission of study data directly to the NRG Oncology SDMC is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account. When submission of supporting documentation to the NRG Oncology SDMC is required, fax to** 412-622-2111. **Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.** |
| 22 | **Appendix B 6.1 Paragraph 2** | 75 | ~~For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.~~ | N/A |

| # | Section | Page(s) | Change | |
|---|---|---|---|---|
| | | | **Version dated December 7, 2010** | **Version dated April 16, 2014** |
| 23 | **Appendix B 6.1 Paragraph 1** | 76 | For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation ~~provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol, (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU~~. | For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation. |
| 24 | **Appendix C Optional NSABP B-42 Registration Program Sample Consent Form** | 77 | There are no changes to the content of the Optional Registration Program Sample Consent Form. The date has been changed to match the most recent version of the protocol. | |
| 25 | **Appendix D NSABP B-42 Sample Consent Form** | 85 | There are no changes to the content of the Sample Consent Form. The date has been changed to match the most recent version of the protocol. | |

# NRG ONCOLOGY
# NSABP PROTOCOL B-42

## A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: Alliance, ECOG-ACRIN, and SWOG


**NRG Oncology**
Two Allegheny Center - Suite 1200
Pittsburgh, PA 15212
**TELEPHONE**: 412-339-5300

**NRG Oncology Statistics and Data Management Center**
One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213
**TELEPHONE**: 412-624-2666
**FAX**: 412-624-1082


**CLINICAL COORDINATING DEPARTMENT: 1-800-477-7227**
**(For Clinical Questions Only)**

**KEY STUDY PERSONNEL:**

| | |
|---|---|
| NRG Oncology Chairman: | Norman Wolmark, MD |
| NRG Oncology Breast Committee Chair: | Eleftherios Mamounas, MD, MPH |
| Protocol Chair: | Eleftherios Mamounas, MD, MPH |
| Protocol Officer: | Barry Lembersky, MD |
| Protocol Statistician: | Jong-Hyeon Jeong, PhD |
| Protocol Pathologist: | Soonmyung Paik, MD |

**Protocol B-42 IND #74,015 (letrozole), sponsored by the NSABP**

| STUDY DRUG | NSC# | DRUG SUPPLY |
|---|---|---|
| Letrozole | 719345 | Novartis Pharmaceuticals Corporation through the NCI |


NCI Version Date: April 16, 2014 (Replaces all other versions)

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# NSABP PROTOCOL B-42

## A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer

| | |
|---|---|
| **Trial Activated:** | August 8, 2006 |
| **Protocol Revision Record** | |
| **Original Version:** | July 12, 2006 |
| **Amendment #1:** | May 30, 2007<br>Sections Changed: Cover Page, Table of Contents, Information Resources, Sections 6.3, 6.3.2, 10.0, Appendix B |
| **Amendment #2:** | September 12, 2007<br>Sections Changed: Cover Page, Information Resources, 2.4, 3.2.2, 4.2.6, 4.2.7, 4.2.8, 4.2.10, 4.2.11, 4.2.12, 4.3.2, 6.1, 6.2, 6.3.1, 7.2.2, 7.3, 7.4, 10.5, 10.7.1, 10.8, 10.9, 11.1, Appendices A, B, C, and D |
| **Amendment #3:** | January 23, 2009<br>Sections Changed: Cover Page, Table of Contents, CTSU Information Resources, Sections 1.0, 4.2.10, 5.0 (Table 1), 12.2, Appendices A, B, C (Cover page), and D (Cover page) |
| **Amendment #4:** | February 4, 2010<br>Sections Changed: Cover Page, Table of Contents, Sections 1.0, 4.0, 5.0, 9.1.2, 9.1.5, 10.1.1, 10.1.3, 10.3.2 (Table 3), 10.5, 12.0, Appendices A, B, C (Cover page), and D (Cover page) |
| **Amendment #5:** | December 7, 2010<br>Sections Changed: Cover Page, Table of Contents, Information Resources, Sections 3.2.5, 8.1.2, 8.2, 9.1.3, 10.2, 10.3, 10.3.2 (Table 3), 10.4, 10.7.1, 10.7.2, 10.8.1, 10.9, 11.6, 14.3, Appendix B |

**Amendment #6:**

April 16, 2014
Throughout the protocol, the following have been changed:

- *The NSABP and the NSABP Operations Center were changed to NRG Oncology where appropriate.*
- *All references to NSABP Biostatistical Center have been changed to NRG Oncology Statistics and Data Management Center (SDMC).*
- *Division has been changed to Department throughout the protocol where appropriate.*
- *References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)."*

Sections Changed: Cover Page, Information Resources, CTSU Information Resources, Sections 9.1.5, 9.1.7, 9.1.8, 9.1.9, 10.3, 10.4, 10.4.1, 10.5, Appendix B, Appendices C (Cover Page) and D (Cover Page)

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## INFORMATION RESOURCES

| NRG Oncology<br>http://www.nsabp.pitt.edu | | |
|---|---|---|
| **NRG Oncology** | Two Allegheny Center – Suite 1200<br>Pittsburgh, PA 15212 | Phone: 412-339-5300 |
| **NRG Oncology Statistics and Data Management Center (SDMC)** | One Sterling Plaza<br>201 North Craig Street, Suite 500<br>Pittsburgh, PA 15213 | Phone: 412-624-2666<br>Fax: 412-624-1082<br>(General office fax) |
| **Questions/problems regarding IRB review & informed consent** | NRG Oncology<br>Department of Regulatory Affairs | Phone: 412-339-5300<br>E-mail: regulatory@nsabp.org |
| **Submission of IRB approval** | CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103 | Phone: 1-866-651-2878<br>Fax: 215-569-0206<br>E-mail:<br>CTSURegulatory@ctsu.coccg.org<br>(for regulatory document submission only) |
| **Questions concerning eligibility and clinical aspects of the trial** | NRG Oncology<br>Clinical Coordinating Department | Phone: 1-800-477-7227<br>E-mail: ccd@nsabp.org |
| **Patient entry information<br>(see Section 12.0)** | NRG Oncology SDMC<br>Patient Entry Coordinator | Phone: 412-383-4900<br>Refer to the Patient Entry Guidelines in the Members' Area of the NSABP Web site. |
| **Questions concerning drug orders, shipments, transfers, and returns (see Section 9.0)** | NRG Oncology SDMC | Phone: 412-624-2666<br>Fax: 412-624-1082 |
| | Pharmaceutical Management Branch<br>***For mail (USPS):***<br>CTEP, DCTD<br>NCI Shady Grove<br>Room 5W228, MSC 9725<br>9609 Medical Center Drive<br>Bethesda, MD 20892-9725<br>***For express courier:***<br>Pharmaceutical Management Branch<br>CTEP, DCTD,<br>NCI Shady Grove<br>Room 5W228, MSC 9725<br>9609 Medical Center Drive<br>Rockville, MD 20850 | Phone: 240-276-6575<br>Fax: 240-276-7893<br>E-mail: PMBAfterHours@mail.nih.gov |
| **Requests for unblinding<br>(including 24-hour emergency unblinding)** | NRG Oncology SDMC | Phone: 412-624-2666<br>Fax: 412-624-1082 |
| **Submission of tumor blocks and unstained sections (see Section 6.0)** | NRG Oncology SDMC<br>One Sterling Plaza<br>201 North Craig Street, Suite 500<br>Pittsburgh, PA 15213<br>***Note: when sending blocks or other materials, please indicate on the package "Pathology Specimens Enclosed".*** | Phone: 412-624-2666<br>Fax: 412-624-1082 |
| **Arrangement for return of blocks that are not to be stored or to request kits for 2 mm core sampling of existing tumor block(s)** | NSABP Division of Pathology | Phone: 412-697-6611<br>E-mail: pathology.questions@nsabp.org |

**INFORMATION RESOURCES (continued)**

| | | |
|---|---|---|
| **Submission of expedited adverse event reports/questions concerning expedited adverse event reporting (see Section 10.0)** | NRG Oncology SDMC<br>B-42 AE Reporting Nurse | Phone: 412-383-2557<br>Fax: 412-622-2113 |
| **Submission of data forms/questions concerning data management** | NRG Oncology SDMC<br>B-42 Data Manager | Phone: 412-624-2666<br>Data fax: 412-622-2111<br>Refer to the B-42 Data Forms page in the Members' Area of the NSABP Web site. |

## Cancer Trials Support Unit (CTSU) Information Resources

*04/16/14*

This study is supported by the NCI CTSU.

Institutions not aligned with NRG Oncology will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix (Appendix B).

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data directly to the NRG Oncology SDMC through the Online Data Entry function unless otherwise specified in the protocol.** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br><br>Phone: 1-866-651-2878<br>Fax: 1-215-569-0206<br>E-mail:<br>CTSURegulatory@ctsu.coccg.org<br>(for regulatory document submission only) | Patient enrollments will be conducted through the Oncology Patient Enrollment Network (OPEN). OPEN is the Web-based registration system for patient enrollments onto NCI-sponsored Cooperative Group clinical trials. Refer to Appendix B for specific instructions. | Submit study data online through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account.<br><br>**NRG Oncology Statistics and Data Management Center**<br>One Sterling Plaza<br>201 North Craig Street, Suite 500<br>Pittsburgh, PA 15213<br><br>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |

**For patient eligibility and treatment-related questions, contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227.**

**<u>For questions unrelated to patient eligibility, treatment, or data submission</u>, contact the CTSU Help Desk by phone or e-mail:**

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**The CTSU Registered Member Web site is located at https://www.ctsu.org**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to Appendix B for specific instructions and documents to be submitted.
- Data management will be performed by the NRG Oncology SDMC. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and other documents** must be sent to the NRG Oncology SDMC unless otherwise directed by the protocol. Do <u>not</u> send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the NRG Oncology SDMC. Please send query responses and delinquent data to the NRG Oncology SDMC and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the NRG Oncology SDMC.

*01/23/09* 1.0 **SUMMARY OF THE STUDY**

*02/04/10* *Note: Accrual closed on January 6, 2010, following achievement of the sample size goal.*

This Phase III randomized, double-blind study will determine if prolonged adjuvant hormonal therapy with letrozole will improve disease-free survival in postmenopausal women with ER-positive and/or PgR-positive tumors who have completed 5 years of hormonal therapy with either 5 years of an aromatase inhibitor (AI) or up to 3 years of tamoxifen followed by an AI. The secondary aims of the study will be to determine whether or not prolonged adjuvant hormonal therapy with letrozole will improve survival, breast cancer-free interval, and distant recurrence. Additional secondary aims will be to determine whether or not prolonged adjuvant letrozole therapy will increase the incidence of osteoporotic-related fractures and arterial thrombotic events.

Women with stage I, II, or IIIA invasive carcinoma of the breast are eligible for this study. Patients will be stratified by pathologic nodal status at the time of diagnosis, use of tamoxifen as adjuvant therapy, and lowest bone mineral density T score in the lumbosacral (LS) spine, total hip, or femoral neck. All patients will be required to have bone mineral density (BMD) and cholesterol testing prior to study entry.

Patients will be randomized to take either letrozole 2.5 mg or placebo orally once a day for 5 years. Calcium and Vitamin D supplementation will be recommended for all patients. Bisphosphonate therapy will be strongly recommended for women who have a T score of -2.0 standard deviations (SD) or less; risk factors for bone fracture and a T score of -1.5 SD or less; or an osteoporotic wrist, spine, or hip fracture.

For patients who have consented to submission of tumor samples, representative blocks from the primary index tumor are required. Serum samples will not be collected for this study.

The proposed sample size for B-42 is 3,840 to be accrued over a period of 5.25 years.

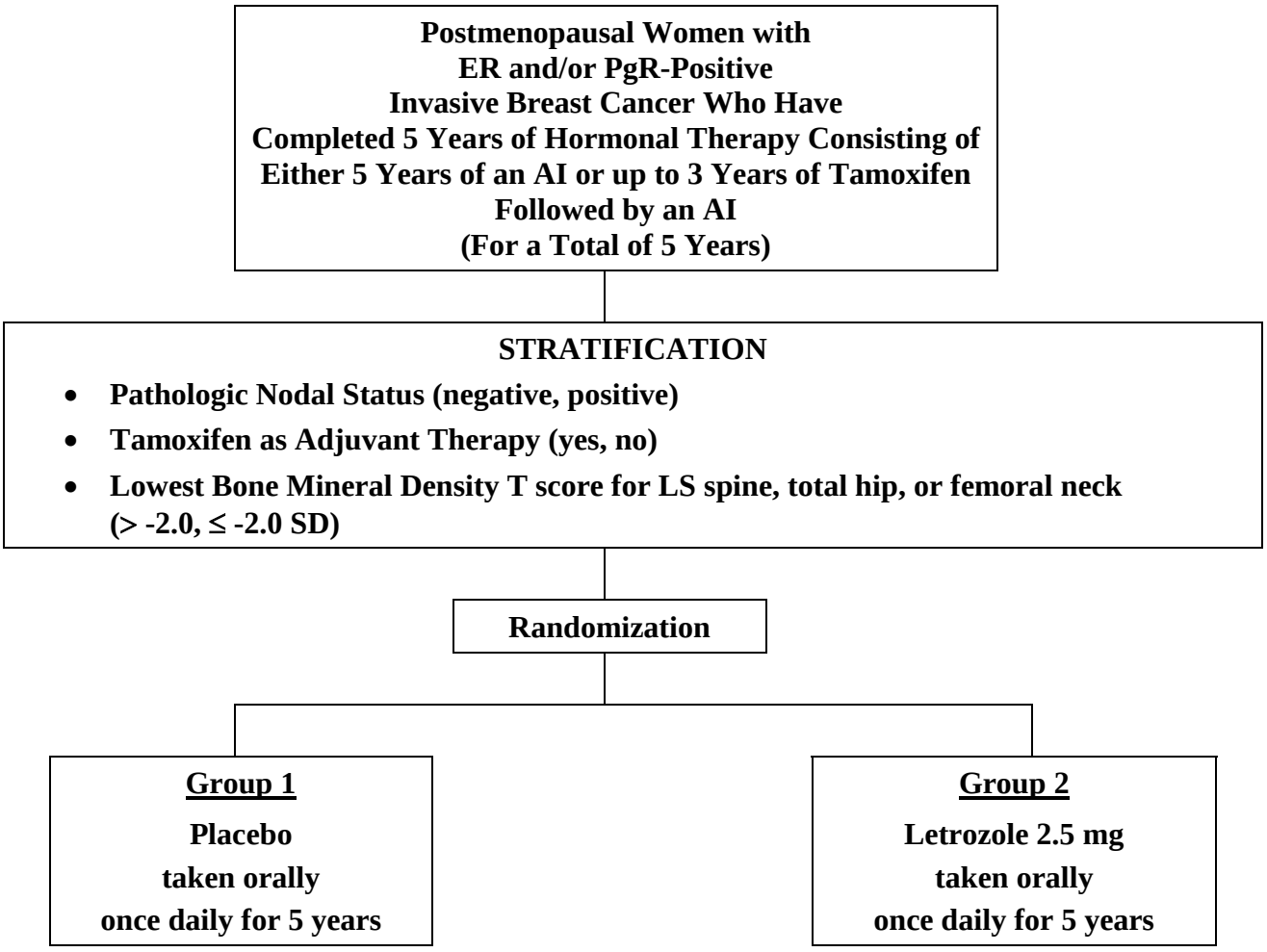
***<u>Optional</u> Letrozole Registration Program for patients who have not yet completed 5 years of initial adjuvant hormonal therapy***

*Note: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment. Accrual and data collection for the NSABP B-42 randomized treatment trial continues as planned.*

In order to have a predominantly letrozole-treated population for B-42 study entry, patients who have taken a minimum of 2 years of hormonal therapy with tamoxifen or an AI may be offered letrozole at no cost until they complete 5 years of initial adjuvant hormonal therapy. See Appendix A for details.

Figure 1

**NSABP B-42 Schema**



## 2.0 BACKGROUND

### 2.1 Rationale for using aromatase inhibitors as adjuvant therapy

Adjuvant hormonal therapy has been shown to significantly improve disease-free and overall survival in patients with resected stage I, II, or III breast cancer.[1-9] For many years, treatment with tamoxifen has been the gold standard for women with hormone receptor-positive tumors. However, recent results from studies evaluating third generation aromatase inhibitors (AIs) as adjuvant therapy in postmenopausal women have challenged the primacy of tamoxifen for this subset of patients.

In patients with advanced breast cancer, the third generation non-steroidal aromatase inhibitors anastrozole and letrozole as well as the steroidal inactivator exemestane have been shown to be superior to megestrol acetate as second-line therapy[10-16] and at least equivalent (and possibly superior) to tamoxifen as first-line therapy.[17-22] Based on these results, several clinical trials have evaluated or are currently evaluating AIs as adjuvant therapy in postmenopausal patients with early-stage breast cancer.

In the adjuvant setting, AIs have demonstrated activity in three distinct clinical situations. In the first situation, an AI was compared to tamoxifen as initial adjuvant hormonal therapy in patients with resected operable breast cancer. The ATAC trial demonstrated that 5 years of anastrozole significantly improved disease-free survival (DFS) when compared to 5 years of tamoxifen.[23,24] More recently, the BIG 1-98 trial also demonstrated improved DFS as well as distant DFS for 5 years of letrozole compared to 5 years of tamoxifen.[25] In the second situation, an AI was compared to tamoxifen in patients who had already received 2-3 years of adjuvant tamoxifen. In three randomized trials (the IES trial [International Exemestane Study], the ABCSG-8/ARNO 95 trial, and the ITA trial [Italian Tamoxifen vs. Anastrozole]), 2-3 years of an AI (exemestane or anastrozole) improved disease-free survival compared to 2-3 years of tamoxifen in patients who had already completed 2-3 years of tamoxifen therapy.[26-28] In the third clinical situation, an AI was evaluated as extended adjuvant hormonal therapy following completion of 5 years of adjuvant tamoxifen. The NCIC MA.17 trial compared 5 years of letrozole with 5 years of placebo in patients who had already completed 5 years of adjuvant tamoxifen and demonstrated significant improvement in disease-free survival in favor of the group which received the AI.[29]

Based on the results from these trials, AIs are increasingly utilized as adjuvant therapy in these three clinical situations. At this time, there are no available results from trials that directly compare these different approaches for using AIs. Thus, the best setting for the adjuvant use of AIs cannot be readily determined at present.

### 2.2 Rationale for evaluating duration of aromatase inhibitor therapy in the adjuvant setting

No data currently exist on the optimal duration of AI therapy. The durations of therapy employed in the above described trials were arbitrarily chosen based on previous experience with tamoxifen (i.e., five years of letrozole in the MA.17 trial) or for purposes of study design (i.e., in order to match the duration of tamoxifen in the ATAC, IES, ABCSG/ARNO and ITA trials). However, even with adjuvant tamoxifen, definitive information on optimal duration was obtained only after several years of its use in the adjuvant setting and for some this may still be an open question.[30] Earlier studies had

shown that prolonging tamoxifen duration up to five years resulted in increased benefit when compared to 1-2 years of administration.[7-9,31] However, when 5 years of tamoxifen were compared to more than 5 years, no additional advantage was demonstrated with the longer duration.[32-34] In fact, in the largest trial that addressed tamoxifen duration, NSABP B-14, a disadvantage was observed in the group of patients who continued tamoxifen for more than 5 years relative to those who discontinued the drug at 5 years (DFS, 78% vs. 82%; p = 0.03; relapse-free survival, 94% vs. 92%; p = 0.13; survival, 94% vs. 91%; p = 0.07, respectively).[32,33] Based on the results with tamoxifen, it is by no means intuitive that prolonging the use of adjuvant AIs would necessarily result in increased benefit when compared to shorter duration.

As the adjuvant use of AIs continues to expand, the question of optimal duration needs to be definitively addressed. Whether less than 5 years of an AI given as upfront adjuvant therapy is as effective as 5 years is a question that is unlikely to be addressed, given that in the pivotal ATAC trial, 5 years of anastrozole were found to be superior to 5 years of tamoxifen. On the other hand, whether prolonged administration of an AI beyond 5 years will result in additional benefit is an important and clinically relevant question that is currently not being addressed in any clinical trial. It is quite possible that resistance to AIs in this setting may develop at different time intervals than resistance to tamoxifen.

Similarly, in the clinical situation where the AI is given for 2-3 years following 2-3 years of adjuvant tamoxifen, it is also unknown whether continuing the AI for more than 2-3 years might result in additional benefit. Although some may use the data from the ATAC trial in order to justify more prolonged use of the AI in this setting (i.e. for 5 years), such decision is based on extrapolation and not on sound clinical data. Furthermore, the results from all six adjuvant trials, reported so far, suggest that the benefit from the AI is realized early on, with a median follow-up of 2.5-3 years from initiation of therapy (33 months in the ATAC trial, 36 months in the BIG 1-98 trial, 33 months in the MA.17 trial, 30.6 months in the IES trial, 28 months in the ABCSG/ARNO trial and 36 months in the ITA trial). Based on the above, there is currently no clinical justification outside of a clinical trial to prolong the administration of the AI for more than 2-3 years if tamoxifen was already given for 2-3 years as upfront therapy.

Finally, no data exist on the optimal duration of AIs when used as extended adjuvant therapy after 5 years of tamoxifen. Five years of therapy was arbitrarily selected in the MA.17 trial but whether shorter therapy could be as effective or whether longer therapy could be more effective are questions that need to be addressed. A small study from the Austrian Breast Cancer Study Group randomized 812 patients who had received 5 years of adjuvant tamoxifen (or tamoxifen and aminoglutethimide) to no further therapy or to 3 years of anastrozole. Results from this study were recently presented at the 2005 meeting of the American Society of Clinical Oncology;[35] with 60 months of median follow-up, anastrozole-treated patients experienced a 36% reduction in recurrence (p = 0.0477) and a 10% reduction in mortality (p = n.s.). These results are concordant to those from the MA. 17 trial, but because of the small sample size of this trial, they are not informative regarding the duration of the AI question. Plans are currently underway from at least two cooperative groups to address this question prospectively. The Austrian Breast Cancer Study Group is currently planning a study comparing 2 years of anastrozole with 5 years of the drug in patients who complete 5 years of adjuvant tamoxifen. On the other hand, the investigators from the NCIC MA.17 trial are planning to compare 5 years with 10 years of letrozole in letrozole-treated patients participating in that trial.[36] The NSABP (in collaboration with the investigators from the MA.17 trial) is

also planning to address the question of 5 vs. 10 years of exemestane after 5 years of tamoxifen in the NSABP B-33 trial. This trial was initially a randomized comparison of 5 years of exemestane vs. 5 years of placebo following 5 years of tamoxifen but was modified to give exemestane to all patients following disclosure of the MA.17 results. However, the setting of extended adjuvant hormonal therapy is not ideal for testing the question of optimal duration of AIs, since the results may not be directly transferable to the setting of AIs as upfront therapy or as therapy after 2-3 years of tamoxifen. For example, if 10 years of AI therapy after 5 years of tamoxifen is not better than 5 years, this may not necessarily be the case when AIs are used as upfront adjuvant therapy (or as adjuvant therapy after 2-3 years of tamoxifen). Furthermore, even by combining the NCIC MA.17 and the NSABP B-33 trial, there may not be enough patients and events to address the question in a definitive manner.

From the above, it is evident that there is a need to definitively address the question of B-42 in a prospective randomized trial either when the AI is given as initial adjuvant therapy or when the AI is used following 2-3 years of adjuvant tamoxifen.

## 2.3 Rationale for the selected approach and trial design

Aromatase inhibitors began to be utilized as adjuvant therapy following the disclosure of the ATAC trial results in December 2001. Thus, the initial group of patients to receive AIs as their adjuvant hormonal therapy will be completing 5 years of therapy by the end of 2006 and could be randomized at that point to either continue the AI or stop. Additionally, some patients who began tamoxifen prior to 2001 chose to convert to an AI based on the ATAC results. Following disclosure of the IES trial in March 2004, an increasing number of patients who receive initial tamoxifen are being switched to an AI for the remainder of their hormonal therapy. Thus, patients will be completing their 5 years of hormonal therapy consisting of at least 2 years of an AI beginning in 2006 and those will also be available for randomization. On the other hand, patients who were put on an AI following 5 years of tamoxifen (following disclosure of the results of the MA.17 trial in October 2003), will not be available for randomization until the end of 2008 (outside of the MA.17 participants) and thus constitute a less attractive group of patients for the present study. Furthermore, the expected lower event rate in these patients between year 10 and year 15 from diagnosis is an additional drawback to including them in this trial. For the above reasons, the trial will be limited to patients from the two former groups.

Since letrozole will be used in this trial, it would be preferable to enroll women who had received letrozole during their initial five years of therapy. In order to have a predominantly letrozole-treated population for randomization, patients who have taken at least 2 years of an AI or tamoxifen (for up to 3 years) will be offered letrozole (at no cost) until they complete 5 total years of hormonal therapy. These patients will then be offered randomization to 5 additional years of letrozole or placebo. Patients who wish to continue on another AI until the 5-year point will also be eligible for B-42. After the completion of 5 years of hormonal therapy which includes an AI other than letrozole, the patient will be offered randomization to 5 years of letrozole or 5 years of placebo.

The proposed trial will provide meaningful clinical information irrespective of its outcome. Obviously, if the longer duration does not result in improved outcome, 5 years of an AI (or 2-3 years of tamoxifen followed by 2-3 years of an AI), would become the optimal duration. If, on the other hand, the longer duration results in improved outcome,

one would have to evaluate the risk vs. benefit ratio of prolonging therapy by taking into account long term toxicity such as osteoporosis and resulting fractures.

*09/12/07* 2.4 **Data from randomized trials evaluating aromatase inhibitors as adjuvant therapy**

The first study to produce results with AIs as adjuvant therapy was the ATAC trial.[23] The ATAC trial aimed to compare the safety and efficacy of tamoxifen with those of anastrozole alone and the combination of anastrozole plus tamoxifen for 5 years. Participants were postmenopausal patients with invasive operable breast cancer who had completed primary therapy and were eligible to receive adjuvant hormonal therapy. The primary endpoints were DFS and occurrence of adverse events. A total of 9,366 patients were recruited, of whom 7,839 (84%) were known to be hormone-receptor-positive. Median follow-up was 33.3 months. DFS at 3 years was 89.4% on anastrozole and 87.4% on tamoxifen (hazard ratio 0.83; 95% CI, 0.71-0.96; p = 0.013). Results with the combination were not significantly different from those with tamoxifen alone (87.2%, 1.02 [0.89-1.18], p = 0.8). The improvement in DFS with anastrozole was seen in the subgroup of hormone-receptor-positive patients, but not the hormone-receptor-negative patients. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio 0.42 [0.22-0.79], p = 0.007). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p = 0.02), vaginal bleeding and discharge (p < 0.0001 for both), cerebrovascular events (p = 0.0006), venous thromboembolic events (p = 0.0006), and hot flushes (p < 0.0001). Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures (p < 0.0001 for both). Based on these results, the authors concluded that anastrozole is an effective and well tolerated endocrine option for the treatment of postmenopausal patients with hormone-sensitive early breast cancer but also that longer follow-up is required before a final benefit vs. risk assessment can be made.

Updated results from the ATAC trial were recently published based on a median follow-up of 47 months.[24] The DFS estimates at 4 years remained significantly more favorable for patients receiving anastrozole compared with those receiving tamoxifen [86.9% vs. 84.5%, respectively, hazard ratio (HR), 0.86; p = 0.03]. The benefit from anastrozole in DFS was again greater in patients with hormone receptor-positive tumors (HR, 0.82; 95% CI, 0.70-0.96; p = 0.014). The HR for time to recurrence also indicated a significant benefit for patients receiving anastrozole compared with those receiving tamoxifen (HR, 0.83; 95% CI, 0.71-0.96; p = 0.015), with additional benefit for patients with hormone receptor-positive tumors (HR, 0.78; 95% CI, 0.65-0.93; p = 0.007). Contralateral breast cancer incidence data also continued to favor anastrozole (odds ratio [OR], 0.62; 95% CI, 0.38-1.02; p = 0.062), and statistical significance was achieved in the hormone receptor-positive subgroup (OR, 0.56; 95% CI, 0.32-0.98; p = 0.042). The updated safety analysis also confirmed the findings of the first analysis, in that endometrial cancer (p = 0.007), vaginal bleeding and discharge (p < 0.001 for both), cerebrovascular events (p < 0.001), venous thromboembolic events (p < 0.001), and hot flashes (p < 0.001) all occurred less frequently in the anastrozole group, whereas musculoskeletal disorders and fractures (p < 0.001 for both) continued to occur less frequently in the tamoxifen group. These results indicated that the favorable safety profile of anastrozole remained consistent.

An even more recent update from the ATAC trial was presented at the 2004 San Antonio Breast Cancer Symposium (and eventually published in Lancet) with 68 months of

median follow-up.[37,38] This update also showed that the benefit from anastrozole in improving disease-free survival continues to persist. At 6 years, hormone-receptor-positive patients treated with anastrozole had a 3.3% absolute improvement in DFS compared to those treated with tamoxifen. At this update, a significant reduction in distant recurrence has also emerged (14% reduction in the intent-to-treat population [p = 0.04] and 16% reduction in the hormone-receptor-positive patients [p = 0.06]). A significant reduction in overall mortality with anastrozole was not evident in this analysis (HR: 0.97, [p = 0.7] for both the intent-to-treat population and hormone-receptor-positive patients) although there was a non-significant trend towards reduction in breast cancer deaths (HR: 0.88 in the intent-to-treat population [p = 0.2] and HR: 0.87 in the hormone-receptor-positive patients [p = 0.2]).

Recently, a second trial reported preliminary results with the use of an aromatase inhibitor as upfront adjuvant hormonal therapy. The first results of IBCSG 18-98 (BIG 1-98) trial were presented at the 2005 St. Gallen Conference and the 2005 ASCO Meeting.[39] That trial, coordinated by the International Breast Cancer Study Group, evaluated letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. In addition to the direct comparison of 5 years of letrozole with 5 years of tamoxifen, two additional arms were included in that trial and those evaluated the sequential administration of 2 years of tamoxifen followed by 3 years of letrozole and the sequential administration of 2 years of letrozole followed by 3 years of tamoxifen. Outcome results comparing the sequential therapy arms to those using upfront tamoxifen or letrozole are not available as of yet. The primary core analysis, presented at the St. Gallen conference and at the ASCO meeting related to the comparison of upfront tamoxifen with upfront letrozole. This primary core analysis included a total of 8010 patients (4003 on letrozole and 4007 on tamoxifen). With a median follow up of 25.8 months, there were a total of 779 DFS events. There was a significant improvement in DFS with letrozole compared to tamoxifen (5-year DFS 84.0% with letrozole vs. 81.4% with tamoxifen, HR: 0.81, p = 0.003). Similarly, there was a statistically significant 27% reduction in distant recurrences with letrozole vs. tamoxifen (HR: 0.73, p = 0.006), and a non-statistically significant 14% reduction in mortality (HR: 0.86, p = 0.16). Compared to tamoxifen, letrozole was associated with an increased risk of bone fractures (5.8% vs. 4.1%) and an increase in hypercholesterolemia (43.6 % vs. 19.2%). On the other hand, letrozole decreased risk of venous thromboembolic side effects (1% vs. 2.4%), vaginal bleeding (3.3% vs. 6.6%) and endometrial biopsies (1.9% vs. 7.2%). Although thromboembolic events were reduced with letrozole, other serious cardiovascular events were slightly increased (3.6% vs. 2.5%).

The second trial to report results with the use of AIs in the adjuvant setting was the NCIC MA.17 trial.[29] This was a double-blind, placebo-controlled trial to test the effectiveness of 5 years of letrozole in postmenopausal breast cancer patients who have completed 5 years of tamoxifen. The primary endpoint was DFS. A total of 5,187 women were enrolled. At the first interim analysis and with a median follow-up of 2.4 years, there was a significant reduction in local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast in the letrozole group (75 events) compared to the placebo group (132 events). The estimated 4-year DFS was 93% and 87%, respectively (p < 0.001). A total of 42 women in the placebo group and 31 women in the letrozole group died (p = 0.25). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There were new diagnoses of patient-reported osteoporosis in 5.8% of the women in the

letrozole group and 4.5% of the women in the placebo group (p = 0.07). However, the rates of fracture were similar. Hypercholesterolemia and cardiovascular events were similar between the two arms. The authors concluded that when compared with placebo, letrozole therapy after the completion of standard tamoxifen treatment significantly improves DFS. Updated results from this trial were recently presented at the 2004 meeting of the American Society of Clinical Oncology. With a median follow-up of 30 months, there continues to be a significant improvement in DFS in favor of letrozole (4-year DFS rate of 94.7% for letrozole vs. 89.8% for placebo, hazard ratio for DFS event: 0.58, p = 0.0004). The effect of letrozole was seen irrespective of nodal status. For node-negative patients, the 4-year DFS was 96.3% for letrozole vs. 93.6% for placebo for an absolute difference of 2.7%. For node-positive patients, the 4-year DFS was 92.3% and 84.8% respectively for an absolute difference of 7.5%. Additionally in this update, a significant improvement in distant DFS was observed in favor of letrozole (p = 0.002) and, more importantly, an overall survival advantage was observed for the node-positive cohort (p = 0.04).

Lastly, there have been three trials reported to date comparing tamoxifen to an AI in patients who had completed 2-3 years of tamoxifen. The first was reported in abstract form by Boccardo et al at the 2003 San Antonio Breast Cancer Symposium.[28] In that trial, postmenopausal patients with hormone-receptor positive, node-positive breast cancer who had received 2-3 years of tamoxifen were randomized to either continue tamoxifen for 3-2 years or to receive anastrozole for the same time period. Major trial endpoints included disease recurrence, second primary tumor (including contralateral breast cancer), and death from any cause. Between March 1998 and December 2002, 448 patients were randomized. Median follow-up time was 36 months (range 1-70). The analysis presented included a total of 62 events (13.8%) and 14 deaths (3.1%). There was a significant reduction in DFS events in favor of anastrozole (loco-regional failure: 13 vs. 2, distant metastases: 19 vs. 10, second primary cancers: 10 vs. 5, deaths without relapse 3 vs. 0). The event-free survival was significantly improved in patients receiving anastrozole compared to those continuing with tamoxifen (p = 0.0002). There was a non-significant trend towards improved overall survival in favor of anastrozole (p = 0.1). There were no significant differences in the rates of most of the major toxicities observed. However, there were significant differences in gastrointestinal symptoms (p = 0.006) and cholesterol levels (p = 0.01) in favor of tamoxifen and significant differences in gynecological symptoms in favor of anastrozole (p = 0.001). No significant differences in the rates of treatment withdrawals were observed between the two groups. Updated results from this trial with 52 months of median follow-up were recently presented at the 2005 ASCO Meeting.[40] They continue to demonstrate a significant improvement in event-free survival (58% reduction in event, p = 0.0001), but no statistically significant improvement in overall survival as of yet (48% reduction in mortality, p = 0.10).

The second trial evaluating AIs in this setting was recently published by Coombes et al.[26] This was a double-blind, randomized trial designed to test whether, after 2-3 years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the 5 years of treatment. The primary endpoint was DFS. A total of 4,742 patients were enrolled. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported – 183 in the exemestane group and 266 in the tamoxifen group. The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 (p < 0.001 by the log-rank test), representing a 32% reduction in risk and

corresponding to an absolute benefit in terms of DFS of 4.7% at 3 years after randomization. Overall survival was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Severe toxic effects of exemestane were rare. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and 9 in the exemestane group ($p = 0.04$). The authors concluded that exemestane therapy after 2-3 years of tamoxifen therapy significantly improved DFS as compared with the standard 5 years of tamoxifen treatment. An update from that trial was also presented at the 2004 San Antonio Breast Cancer Symposium with a median follow up of 37.4 months.[41] A total of 615 DFS events and 339 deaths were included in that analysis. The benefit in favor of exemestane continues to persist. There was a 27% reduction in DFS event (HR: 0.73, $p = 0.0001$) and a 30% reduction in recurrence (HR: 0.70, $p = 0.00005$). No significant improvement in overall survival was noted as of yet in this trial, although there was a non-significant trend in favor of the exemestane-treated patients.

The third trial, comparing anastrozole with tamoxifen in patients who have completed two years of tamoxifen was reported at the 2004 San Antonio Breast Cancer Symposium.[27] This was a combined analysis of the ABCSG-8 trial (Austrian Breast Cancer Study Group) and the ARNO-95 trial. A total of 3,224 patients were randomized (1,606 to tamoxifen and 1,618 to anastrozole). With 28 months of median follow up there was a significant improvement in the 3-year DFS in favor of anastrozole (95.8% vs. 92.7%, HR: 0.60, $p = 0.0009$). Similarly, there was a statistically significant 39% reduction in distant recurrences with anastrozole vs. tamoxifen (HR: 0.61, $p = 0.0067$), and a non-statistically significant 24% reduction in mortality (HR: 0.76, $p = 0.16$). The benefits of switching to anastrozole were seen regardless of baseline prognostic factors. Both treatments were well tolerated. The incidence of pre-specified side effects was low in both groups. As expected, there were significantly more fractures in patients switching to anastrozole (2.4%) vs. in those who continued on tamoxifen (1.2%). No significant difference between treatments was seen in gynecological side effects because, as seen in the ATAC trial, these generally occurred soon after starting tamoxifen.

## 3.0 STUDY AIMS AND ENDPOINTS

### 3.1 Primary aim and endpoint

The *primary aim* is to determine whether or not prolonged adjuvant hormonal therapy with letrozole will improve disease-free survival in postmenopausal women with ER-positive and/or PgR-positive tumors who have completed 5 years of hormonal therapy with 5 years of an aromatase inhibitor (AI) or 5 years of a combination of up to 3 years of tamoxifen followed by an AI.

The *primary endpoint* for analysis is disease-free survival (DFS). DFS events are local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (IBTR), regional recurrence, distant recurrence, second primary cancer (other than squamous and basal cell carcinoma of the skin, melanoma in situ, and carcinoma in situ of the colon and cervix), and death from any cause prior to recurrence or second primary cancer.

### 3.2 Secondary aims and endpoints

#### 3.2.1 ***Survival (S)***

*Aim:* Determine whether or not prolonged adjuvant hormonal therapy with letrozole will improve survival.

*Endpoint:* Time from randomization to death from any cause.

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#### 3.2.2 ***Breast cancer-free interval***

*Aim:* Determine whether or not prolonged adjuvant hormonal therapy with letrozole will improve breast cancer-free interval.

*Endpoint:* Time from randomization to recurrence or contralateral second primary breast cancer. Other second primary cancers and death without evidence of recurrent disease will be treated as censored events in this case.

#### 3.2.3 ***Distant recurrence***

*Aim:* Determine whether or not prolonged hormonal therapy with letrozole will improve distant recurrence.

*Endpoint:* Time from randomization to distant recurrence of breast cancer.

#### 3.2.4 ***Osteoporotic-related fractures (Colles', hip, and spine)***

*Aim:* Determine whether or not prolonged adjuvant hormonal therapy with letrozole will increase osteoporotic-related fractures (Colles', hip, and spine).

*Endpoint:* Incidence of osteoporotic fractures (Colles', hip, and spine).

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#### 3.2.5 ***Arterial thrombotic events***

*Aim:* Determine whether or not prolonged adjuvant hormonal therapy with letrozole will increase arterial thrombotic events.

*Endpoint:* Incidence of arterial thrombotic events defined in CTCAE v4.0 as ≥ grade 1 stroke, transient ischemic attacks; ≥ grade 2 acute coronary syndrome, ischemia cerebrovascular; ≥ grade 3 myocardial infarction, peripheral ischemia, visceral arterial ischemia; and ≥ grade 4 selected thromboembolic events (cerebrovascular event, arterial insufficiency).

## 4.0 ELIGIBILITY AND INELIGIBILITY

*02/04/10* *Note: Accrual closed on January 6, 2010, following achievement of the sample size goal.*

### 4.1 Patient selection guidelines

*The guidelines in Section 4.1 will **not** be considered exclusion criteria; however, in addition to the formal eligibility/ineligibility criteria in Sections 4.2 and 4.3, investigators should consider each of these factors when selecting patients for B-42. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy when deciding if a patient is appropriate for B-42. These considerations should be weighed carefully, as they may make a patient an unsuitable candidate for B-42 and may increase risk to the patient:*

- Patients with a life expectancy less than 10 years, excluding her diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)

- Patients who have demonstrated poor compliance with previous AI or tamoxifen and AI therapy. *(Note: Patients may have had drug holidays, as long as the frequency or duration of the drug holidays does not indicate to the investigator that the patient will not be compliant with taking study drug for 5 years.)*

- Patients for whom bisphosphonate therapy is not recommended or not tolerated. *(Note: Bisphosphonate therapy is a recommended intervention in the B-42 osteoporosis management instructions.)*

- Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

### 4.2 Conditions for patient eligibility

Patients who satisfy all of the following conditions are the only patients who will be considered eligible for the study:

4.2.1 The patient must have consented to participate and must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines.

4.2.2 Patients must be female.

4.2.3 Patients must have an ECOG performance status of 0 or 1 (0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory).

4.2.4 Patients must be postmenopausal at the time of randomization. *(Note: Premenopausal or perimenopausal women requiring therapy with luteinizing hormone-releasing hormone [LHRH] analogs to suppress ovarian function are not eligible.)*

For study purposes, postmenopausal is defined as:

- age 56 or older with no spontaneous menses for at least 12 months prior to study entry, **or**
- age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) AND with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standards, **or**
- a prior documented bilateral oophorectomy.

4.2.5 The patient must have remained disease-free from the time of initial breast cancer diagnosis until the time of randomization.

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4.2.6 The patient must have had histologically-confirmed invasive carcinoma of the breast by diagnostic core needle biopsy or by final pathologic evaluation of the surgical specimen.

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4.2.7 Patients who received neoadjuvant chemotherapy must have been clinical Stage I, II, or IIIA. For patients who received adjuvant chemotherapy, the primary tumor must have been T1-3 on pathologic evaluation and ipsilateral nodes must have been pN0, pN1 ($pN1_{mi}$, $pN1_a$, $pN1_b$, $pN1_c$), $pN2_a$, $pN3_a$, or $pN3_b$. Refer to the Members' Area of the NSABP Web site for TNM nomenclature and staging information.

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4.2.8 The primary tumor must have been ER-positive and/or PgR-positive. (Patients who had a tumor that was considered to be borderline for hormone receptor positivity and who were treated with tamoxifen and/or an AI are eligible for this study.)

4.2.9 Patients must have undergone either a lumpectomy with axillary nodal staging followed by breast radiotherapy or a total mastectomy with axillary nodal staging. (Acceptable axillary nodal staging procedures include sentinel node biopsy alone, if sentinel nodes were negative on H&E staining.)

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4.2.10 The duration of the patient's hormonal therapy following breast cancer diagnosis must have been 57-63 months from the first dose regardless of the number of missed doses. Hormonal therapy must have consisted of an AI *or* a combination of up to 3 years of tamoxifen followed by an AI. *Tamoxifen may not have been given during years 4 and 5 of the 5 years of adjuvant hormonal therapy. (Note: Patients must discontinue their adjuvant AI therapy at the time of randomization.)*

***<u>Optional</u> Letrozole Registration Program for patients who have not yet completed 5 years of hormonal therapy***

*Note: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment. Accrual and data collection for the NSABP B-42 randomized treatment trial continues as planned.*

In order to have a predominantly letrozole-treated population for B-42 study entry, patients who have had a minimum of 2 years of hormonal therapy and who are currently on tamoxifen (for up to 3 years) or an AI may be offered letrozole at no cost until they complete 5 total years of initial adjuvant hormonal therapy. See Appendix A for instructions on enrolling patients on this **optional** Letrozole Registration Program.

*09/12/07* 4.2.11 B-42 randomization must be within 6 months following completion of 5 years (57-63 months) of initial adjuvant hormonal therapy.

*09/12/07* 4.2.12 At the time of randomization, the patient must have had the following:

- history and physical exam within 3 months demonstrating no findings suggestive of recurrent breast cancer;
- bilateral mammogram within 1 year (unilateral if patient had a mastectomy); mammogram not required if patient had a ***prophylactic*** contralateral mastectomy;
- bone mineral density (BMD) testing within 1 year; and
- fasting lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides) with a total cholesterol value ≤ grade 1 (according to CTCAE v3.0), with or without cholesterol-lowering therapy.
  - ***within 1 year*** if the patient has a history of hypercholesterolemia controlled with cholesterol-lowering therapy and/or therapeutic lifestyle changes ***or*** if the patient has a history of one or more of the following risk factors for future cardiovascular events: diabetes, hypertension, obesity, tobacco use, hypertriglyceridemia, documented coronary artery disease, or family history of premature coronary heart disease.
  - ***within 2 years*** for all other patients.

*Note: For information regarding management of blood cholesterol, refer to Section 8.1.*

### 4.3 Conditions for patient ineligibility

Patients with one or more of the following conditions will be ineligible for this study:

4.3.1 History of non-traumatic osteoporotic fracture of wrist, hip, or spine.

*09/12/07* 4.3.2 Diagnosis of bilateral breast cancer including DCIS (synchronous or metachronous).

4.3.3 Other malignancies unless the patient is considered to be disease-free for 5 or more years prior to randomization, and is deemed by their physician to be at low risk for recurrence. Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: carcinoma in situ of the cervix, colon carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.

4.3.4 Sex hormonal therapy, e.g., estrogen- or progesterone-replacement therapy or oral contraceptives. *These patients are eligible only if this therapy is discontinued prior to randomization.* (See Section 7.3 for exceptions.)

4.3.5 Therapy with any hormonal agent such as raloxifene for management of osteoporosis. *Patients are eligible only if these medications are discontinued prior to study entry.*

4.3.6 Administration of any investigational agent within 30 days before study entry.

## 5.0 **REQUIRED ENTRY AND FOLLOW-UP STUDIES**

*Note: Accrual closed on January 6, 2010, following achievement of the sample size goal.*

TABLE 1. Studies required for B-42 study entry and during and after study therapy

| Required studies[a] | Prior to randomization | Within 3 months after randomization | From randomization through Year 5 (during therapy)[b] | Years 6 and 7 | Years 8+ |
|---|---|---|---|---|---|
| History & physical exam **(including height and weight)** | X (within 3 months) | | X (every 12 months)[c] | | |
| Assessment of cardiac risk factors | X (within 3 months) | | | | |
| Patient status update | | | X (every 6 months)[c] | X (every 12 months)[d] | X (every 12 months)[e] |
| Adverse event assessment | | | X (every 6 months) | X (6 months after last dose) | |
| Fasting lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides) | X (within 1-2 years)[f] | | X[g] | | |
| Bilateral mammogram (unilateral if mastectomy) | X (within 12 months) | | X (every 12 months)[h] | X (every 12 months) | X (every 12 months) |
| Bone mineral density (BMD) testing | X (within 12 months) | | X (every 2 years)[i] | | |
| Tumor block collection (patients who have consented)[j] | | X | | | |

**a** H&P, laboratory testing, and other tests/exams may be performed more frequently at the discretion of the investigator.

**b** If the study drug is discontinued before completion of 5 years of therapy, follow the schedule for Years 6+, with the exception of the patient status update, which will continue every 6 months through year 5. BMD testing is at the investigator's discretion; see footnote **i**. (Reminder: A final AE assessment must be performed 6 months after the last dose.)

**c** Determine if the patient is alive and disease-free; assess adverse events, arterial thrombotic events (see Section 3.2.5), osteoporotic bone fractures (see Section 3.2.4), bisphosphonate use, lipid therapy, and study drug compliance. This should be done at the time of the annual H&P exam and at the 6-month points between the H&P exams. When not done at the annual H&P exam, patient status update assessments may be conducted at an office visit or by telephone contact with the patient.

**d** Determine if the patient is alive and disease-free; assess arterial thrombotic events (see Section 3.2.5), osteoporotic bone fractures (see Section 3.2.4), bisphosphonate use, and lipid therapy. May be conducted at an office visit or by telephone contact with the patient.

**e** Determine if the patient is alive and disease-free; assess arterial thrombotic events (see Section 3.2.5), and osteoporotic bone fractures (see Section 3.2.4). May be conducted at an office visit or by telephone contact with the patient.

**f** Must be performed *within 1 year* for patients with a history of hypercholesterolemia or other risk factors for future cardiovascular events (see Section 4.2.12); *within 2 years* for patients with no cardiovascular risk factors and no history of hypercholesterolemia.

**g** Lipid panel testing should be done as follows:

- For patients with < grade 1 cholesterol and no risk factors at study entry and during therapy (see Section 4.2.12), frequency of subsequent testing is at the discretion of the investigator.
- For patients with < grade 1 cholesterol but who have any of the risk factors listed in Section 4.2.12, testing should be performed at least every 2 years.
- For patients with grade 1 hypercholesterolemia, testing should be performed at least yearly.
- For patients whose study drug has been held for ≥ grade 2 cholesterol, testing should be performed more frequently to determine the feasibility of resuming study drug within 6 months (see Section 8.1.2).
- If hypercholesterolemia or hypertriglyceridemia is detected, further evaluation should be based on the current National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) guidelines (see Section 8.1).

**h** The first mammogram must be 12 months following the most recent mammogram performed prior to randomization; then every 12 months.

**i** The first BMD test must be performed 2 years after the most recent BMD test performed before study entry; then every 2 years. At the investigator's discretion, BMD testing may be performed more frequently. It is recommended that women who are osteopenic with T score of ≤ -1.5 SD have BMD testing every 12 months.

**j** Blocks from the primary index tumor (or positive lymph node if the primary tumor block is not readily available).

*04/16/14* 6.0 **PATHOLOGY AND CORRELATIVE STUDIES**

NSABP B-42 requires the collection and submission of tumor samples. However, individual patients may always refuse the collection, storage, and use of their tissues by answering "No" to the appropriate questions in the consent form. These patients may still participate in the trial; however, tumor samples must **not** be submitted for patients who have answered "No" to the first two of the three questions (Question #1 and #2 as presented in the NSABP Sample Consent Form [Appendix D]). If the patient answered "Yes" to either question (Question #1 or #2), a sample must be submitted.

**NOTE:** The tissue samples collected in this study will be used for B-42 studies as described in Section 6.2, as well as for other future unspecified correlative studies. ***The specimens procured will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used.*** Central review of a patient's tumor pathology and markers examined will not be reported to the patient or her physician and will not have any bearing on her treatment.

Submitted slides and blocks are initially shipped to and logged into the database at the NRG Oncology SDMC (refer to Information Resources, page 9). These samples are then stripped of patient identifiers except NSABP study numbers and forwarded to the NSABP Division of Pathology where they are assigned a code number for further processing and study. Three replica tissue microarrays of 0.6 mm cores will be constructed from collected blocks.

*09/12/07* 6.1 **Summary of pathology requirements (See Section 6.3)**

TABLE 2. Summary of B-42 tissue submission requirements

| | **Within 3 months following randomization** |
|---|---|
| **Paraffin blocks** | Representative blocks from the primary index tumor; if primary tumor block is not readily available, submit blocks from positive lymph node.**a,b** |
| **Diagnostic H & E slides** | No |
| **Blood/serum** | No |

**a** For patients who have consented to specimen collection.
**b** Alternative submission – 2 mm core sampling of tumor block plus 20-30 unstained sections (mounted on charged slides) from tumor and/or positive node.

*09/12/07* 6.2 **Correlative science studies**

There is no a priori hypothesis for this effort. We will be banking paraffin blocks from the primary tumor (or positive lymph node) in order to have an opportunity to evaluate promising markers in the future, if they become available.

At this point, there are some data that suggest a differential benefit from AI over tamoxifen based on the molecular profile of tumor cells. In the ER+/PR+ subgroup in the ATAC trial (n = 3834), the hazard rate (HR) for anastrozole vs tamoxifen was 0.83, and in the ER+/PR- subgroup (n = 880), the HR was 0.45.[42] For HER2-positive tumors in the IMPACT trial, the clinical response rate was 58% for anastrozole and 22% for tamoxifen.[43] In the P024 trial of neoadjuvant tamoxifen vs letrozole led by Matthew Ellis, the response rate for HER2-positive tumors was 88% for letrozole and 21% for

tamoxifen, and in HER2-negative tumors, the response rate was 55% and 44%, respectively.[44]

These data suggest that a certain subset of breast cancer patients might not derive maximum benefit from 5 years of tamoxifen, and derive greater benefit from an AI. It could be hypothesized that such patients may derive greater benefit if the AI is given for a longer duration. We will examine ER, PR, and HER2 by standardized central assays (ER and PR using the FDA-approved Dakocytomation kit, and HER2 by PathVysion FISH assay). We will explore quantitation of ER and PR by an image analysis program (Cellenger) to examine the correlation between expression levels and benefit from the longer duration of an AI. Abnormalities involving cofactors for ER signaling such as AIB1 may result in resistance to tamoxifen but not to the AI. Patients with such tumors can be hypothesized to benefit even more with a longer duration of AI. Such factors will also be examined using tissue microarray.

Recently, our group has demonstrated that in NSABP B-14, the ER mRNA expression level correlates with clinical benefit from 5 years of tamoxifen with almost log linear correlation between ER mRNA level and benefit from tamoxifen, even when the tumors are positive for ER by binding assay (over 10 fmole). It can be hypothesized that patients with tumors with lower levels of ER mRNA may benefit from an AI and especially with longer duration of an AI. We plan to look at ER mRNA levels with the best methods available in the future.

We are exploring methods of RNA expression profiling. If we find a reliable method of RNA amplification, we will explore microarray gene expression profiling if funding becomes available.

## 6.3 Submission of paraffin blocks

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### 6.3.1 *Tissue requirements*

Representative blocks from the primary index tumor (or positive lymph node if primary tumor block is not available) are required.

*Alternative submission*

While it is desirable that tissue blocks are submitted, for institutions that do not allow submission of the tissue blocks, we recommend submitting the following two items as a substitute:

- 20 to 30 unstained sections of 4-5 micron thickness mounted on charged slides (do not oven bake slides); and
- a 2 mm core sampling of the existing tumor block from a tumor cell-rich area or a similar size fragment cut from the original block. (Tumor block sampling kits can be obtained from the NSABP Division of Pathology [see Information Resources on page 9]).

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*04/16/14*

### 6.3.2 *Tissue submission instructions*

Submit tissue and specimen transmittal form to the NRG Oncology SDMC at the address listed under Information Resources (see page 9).

## 7.0 TREATMENT REGIMEN

### 7.1 Letrozole/placebo instructions

Letrozole 2.5 mg/placebo tablet will be taken orally once daily for 5 years. Letrozole/placebo may be taken without regard to meals.

Letrozole/placebo should begin within 30 days following randomization and is to be given continuously for 5 years. ***Letrozole/placebo will end 5 years from the date of the first dose of letrozole/placebo regardless of any missed doses***.

### 7.2 Osteoporosis management

***All patients should be evaluated clinically for osteoporosis and fracture risks. For detailed information regarding major risk factors for osteoporosis and related fractures, refer to the National Osteoporosis Foundation (NOF) Web site at http://www.nof.org.***

7.2.1 *Bone mineral density (BMD) testing is required every 2 years for all patients while taking study drug.* At the investigator's discretion, BMD testing may be done more frequently. It is recommended that patients who are osteopenic with T score ≤ -1.5 SD have BMD testing every 12 months. (Refer to Section 8.3 for instructions regarding discontinuation of study drug.)

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7.2.2 Osteoporosis management recommendations

- Calcium supplement 500-600 mg po given BID is recommended for all patients.
- Vitamin D 800-1000 IU po once daily is recommended for all patients.
- Bisphosphonate therapy is recommended for women who meet any of the criteria below:
  - T score of -2.0 SD or less
  - Risk factors for bone fracture (refer to the NOF Web site) and T score of -1.5 SD or less
  - Osteoporotic wrist, spine, or hip fracture (occurring after study entry)

  ***Specific agent is at investigator's discretion. Bisphosphonate therapy dose must be the dose recommended for bone protection, not the dose recommended for anti-cancer therapy.***
- Additional interventions recommended for all patients include weight-bearing exercise and resistance exercise.

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## 7.3 Postmenopausal hormonal therapy

Non-hormonal therapy interventions (e.g., Astroglide® or Replens®), *instead of hormonal therapy,* are strongly encouraged for management of postmenopausal vaginal symptoms. *Although the use of topical vaginal hormonal therapies is not encouraged,* at the investigator's discretion, conjugated estrogen ring (Estring®) is permitted.

Refer to Section 7.4.1 for prohibited hormonal therapy.

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## 7.4 Non-protocol therapy guidelines

The following types of treatment, in addition to ***any cancer therapy other than that specified in the protocol***, are prohibited until the time of diagnosis of the first breast cancer recurrence or second primary cancer.

### 7.4.1 *Hormonal therapy*

Patients may ***not*** receive any of the following types of hormonal therapy:

- Selective estrogen receptor modulators (SERMs) for example, raloxifene (Evista®).
- Sex hormonal therapy, e.g., estrogen- or progesterone-replacement therapy (including low-dose estrogen in the form of vaginal cream) and oral contraceptives.
- Femring®.
- Vagifem®.
- Luteinizing hormone-releasing hormone (LHRH) agonists/antagonists (e.g., Zoladex®).
- Aromatase inhibitors.

### 7.4.2 *Participation in other clinical trials*

Patients may not participate in clinical trials employing an investigational agent.

If a B-42 patient is considering participation in another clinical trial (including supportive therapy trials), contact the NRG Oncology Clinical Coordinating Department (see Information Resources on page 9).

## 8.0 CONDITIONS REQUIRING DELAYS OR DISCONTINUATION OF STUDY DRUG

### 8.1 Elevated total cholesterol

#### 8.1.1 *Recommendations for management of blood cholesterol*

Evaluation and clinical management of elevated blood cholesterol is strongly encouraged and should be based on the most recent version and updates of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III or later version).

The most recent clinical guidelines of the NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or later) are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu. (CTSU investigators should refer to the NSABP B-42 web page located on the CTSU Registered Member site.)

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#### 8.1.2 *Management of study drug*

Management of study drug following documentation of elevated total cholesterol, based on CTCAE v4.0 criteria, should be as follows:

- Grade 1
  - Study drug should continue.
  - Lipid profile should be monitored according to the most recent ATP guidelines.

- Grade 2
  - Study drug may continue at the physician's discretion.
  - Lipid profile should be monitored according to the most recent ATP guidelines.
  - If study therapy was held, study drug should resume *if total cholesterol improves to ≤ grade 1*.
  - If grade 2 hypercholesterolemia persists for 6 months despite cholesterol-lowering therapy based on the most recent ATP guidelines, study drug should be permanently discontinued.

- Grade 3 or grade 4
  - Hold study drug.
  - Lipid profile should be monitored according to the most recent ATP guidelines.
  - If total cholesterol returns to ≤ grade 1, study drug may be resumed at the investigator's discretion.
  - If total cholesterol does not return to ≤ grade 1 within 6 months despite cholesterol-lowering therapy based on the most recent ATP guidelines, study drug should be permanently discontinued.

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## 8.2 Arterial thrombotic events

For B-42, ***study drug must be discontinued*** for arterial thrombotic events defined in CTCAE v4.0 as:

- ≥ grade 1
  - stroke
  - transient ischemic attack
- ≥ grade 2
  - acute coronary syndrome
  - ischemia cerebrovascular
- ≥ grade 3
  - myocardial infarction
  - peripheral ischemia
  - visceral arterial ischemia

## 8.3 Osteoporosis

### 8.3.1 *Conditions for which the investigator should consider discontinuation of study drug*

For asymptomatic (without fracture) decline in T-score of -0.5 SD or more ***into or within*** the osteoporotic range (less than -2.5) while on bisphosphonates or other medication for osteoporosis, ***study drug may be discontinued at the investigator's discretion***.

### 8.3.2 *Conditions for which the investigator must discontinue study drug*

If osteoporotic fracture occurs with a T-score less than -2.5 while on bisphosphonates or other medication for osteoporosis, ***study drug must be discontinued***.

## 8.4 Breast cancer recurrence or second primary cancer

Study drug must be discontinued following diagnosis of breast cancer recurrence or diagnosis of a second primary cancer (other than carcinoma in situ of the cervix, colon carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinoma of the skin).

## 8.5 Other adverse events

Dose delays or discontinuations for other adverse events are at the investigator's discretion.

## 9.0 DRUG INFORMATION

### 9.1 Letrozole/placebo

Please refer to the current FDA-approved package insert or the Physicians' Desk Reference for additional information on letrozole.

#### 9.1.1 *Description*

Letrozole is a non-steroidal aromatase inhibitor. It is a white to yellowish crystalline powder that is supplied in tablet form. Each tablet contains letrozole 2.5 mg, cellulose compounds, corn starch, iron oxide, lactose, magnesium stearate, polyethylene glycol, sodium starch glycolate, silicon dioxide, talc, and titanium dioxide.

*02/04/10*

#### 9.1.2 *Storage*

Letrozole tablets should not be stored above 30°C (86°F). Protect from moisture.

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#### 9.1.3 *Toxicities*

Note: The adverse events listed below were experienced by patients in the adjuvant therapy setting.

- *Cardiac disorders:* Acute coronary syndrome; myocardial infarction
- *General disorders:* Fatigue; malaise
- *Gastrointestinal disorders:* Constipation; diarrhea; edema: limb; nausea
- *Investigations:* Cholesterol, high
- *Metabolism and nutritional disorders:* Anorexia
- *Musculoskeletal and connective tissue disorders:* Fracture; osteoporosis; back pain; pain in extremity
- *Nervous system disorders:* Dizziness; headache; lethargy; somnolence
- *Psychiatric disorders:* Depression; insomnia
- *Skin and subcutaneous tissue disorders:* Alopecia; hyperhidrosis
- *Reproductive system and breast disorders:* Vaginal dryness; vaginal hemorrhage
- *Respiratory, thoracic, and mediastinal disorders:* Dyspnea
- *Vascular disorders:* Hot flashes; thromboembolic events

#### 9.1.4 *Precautions/warnings*

No dosage adjustment is required for patients with renal impairment if creatinine clearance ≥ 10 mL/min or for patients with mild to moderate hepatic dysfunction. Elimination of letrozole is mainly hepatic, so patients with hepatic dysfunction should be observed closely for adverse events.

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### 9.1.5 ***Drug supply***

Letrozole (2.5 mg tablets of Femara®) and matching placebo will be provided free of charge by Novartis Pharmaceuticals Corporation and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Letrozole (NSC #719345) and matching placebo will be supplied in bottles containing 110 – 2.5 mg tablets with child-resistant caps and tamper-evident seals. Each bottle represents a 3-month supply of drug, and each patient will receive a total of 20 bottles over 5 years. Each bottle will be labeled with:

- the protocol number (i.e., 'NSABP B-42')
- the patient study number (e.g., 'XX-9999-123,' which is a randomly assigned sequence number)
- the patient initials (e.g., 'LFM'; for NSABP B-42, this will be last initial, first initial, middle initial)
- the bottle number (e.g., 'Bottle 1 of 20,' 'Bottle 2 of 20,' etc.)
- the number of tablets (i.e., '110 tablets')
- agent identification (i.e., 'letrozole 2.5 mg or placebo')
- administration instructions (i.e., 'Take one tablet once daily')
- storage instructions (i.e., 'Do Not Store Above 30°C [86°F]. Protect From Moisture.')
- emergency contact instructions
- a Julian date.

In addition, the bottle labels will have a line for the individual dispensing the medication to enter the patient's name.

The Julian date indicates the day the bottle was shipped and is composed of the last two digits of the calendar year (e.g., 2006 = 06, 2007 = 07) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle shipped on January 1, 2006, would have a Julian date of 06001, and a bottle shipped on December 31, 2007, would have a Julian date of 07365. The Julian date will be used for recalls. When a lot expires, the PMB will determine the last date on which that lot was shipped and will recall everything shipped on or before that date, thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

*04/16/14* 9.1.6 ***Drug procurement for all investigators***

*Note: This information applies to drug orders for patients randomized to letrozole/placebo as part of the B-42 randomized study. For letrozole drug orders for patients participating in the Registration Program of the study, see Appendix A, Section 6.0.*

***No blinded starter supplies will be available for this study.*** Once a patient has been registered with the NRG Oncology SDMC, the NRG Oncology SDMC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the NRG Oncology SDMC the day the patient is registered. It will be processed by the PMB the next business day and shipped the following business day. The initial shipment for each patient will be sent by US Priority Mail (generally 2-3 day delivery) for US sites and by FedEx (generally 1-2 days delivery) for Canadian sites. Thus, if a patient is registered on Monday, the NRG Oncology SDMC would enter a clinical drug request for that patient on Monday and the PMB would process the request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order either Friday or Monday, and Canadian sites could expect to receive their order either Thursday or Friday.

All bottles will be sent to the treating investigator (unless otherwise specified by the local institution). The responsible investigator at each participating institution must be registered with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF). Sites may ship drug directly to the patient if necessary, but not to another physician's office. If shipping drug to the patient, it is recommended that a mail service that tracks the package and provides a return receipt be used (e.g., certified mail, FedEx). The initial request will be for 2 bottles each containing 110 tablets of letrozole or matching placebo (i.e., a 6 month supply) and will be labeled "Bottle 1 of 20" through "Bottle 2 of 20". In addition, approximately 5 months after the patient is randomized (i.e., 1 month before needed), Bottles 3 through 4 will be automatically ordered by the NRG Oncology SDMC. Every 6 months thereafter (always approximately 1 month before needed), the next set of 2 bottles will be automatically ordered by the NRG Oncology SDMC and sent to the treating investigator (unless otherwise specified by the local institution) that enrolled the patient **unless a treatment form, indicating that the patient has discontinued study medication, has been received by the NRG Oncology SDMC**. Due to the NRG Oncology SDMC's automated drug ordering system, study personnel will not be required to submit an NCI Clinical Drug Request Form to obtain NSABP B-42 study drug.

*04/16/14* 9.1.7 ***Drug transfers***

Bottles **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 institution to another participating institution) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., 'XX-9999-123') and the patient's initials (e.g., 'LFM') should be entered in the 'Received on NCI Protocol Number' and the 'Transferred to NCI Protocol Number' fields in addition to the protocol number (i.e., 'NSABP B-42'). The participating institution should also inform the NRG Oncology SDMC of the transfer.

*04/16/14* 9.1.8 ***Drug returns***

**Only undispensed drug supplies should be returned to the NCI Clinical Repository.** When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment or expired bottles recalled by the PMB), investigators should return the study drug to the NCI Clinical Repository using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., 'XX-9999-123') and the patient's initials (e.g., 'LFM') should be entered in the 'Lot Number' field. A separate line item is required for **each** patient ID and for **each** agent. **Opened bottles with remaining tablets should be documented in the patient-specific investigational agent accountability record (i.e., logged in as "returned by patient" and logged out as "for destruction") and destroyed on-site in accordance with institutional policy.**

*04/16/14* 9.1.9 ***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 CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate investigational agent accountability record must be maintained for each patient ID number (e.g., 'XX-9999-123') on this protocol.

## 9.2 Unblinding

### 9.2.1 *Conditions for unblinding*

Protocol medication will be unblinded when knowledge concerning the medication the patient is receiving will influence future treatment.

*04/16/14* 9.2.2 ***Procedures for unblinding***

When unblinding is required, local investigators must telephone the NRG Oncology SDMC (see Information Resources on page 9) and state that they wish to unblind a patient. The same procedure applies to 24-hour emergency unblinding. A data file is maintained for the study and can be accessed by a limited number of designees within the NRG Oncology SDMC who serve the study in an administrative, nonclinical capacity. NRG Oncology SDMC personnel will require the protocol number (i.e., 'NSABP B-42'), the patient's ID number (e.g., 'XX-9999-123'), the patient's initials (e.g., 'LFM'), and the reason for the unblinding request in order to unblind the patient. After the confirmation of the indication for unblinding is obtained, the NRG Oncology investigator will be notified immediately of the patient's treatment assignment. A computer record will be created to identify the patient as having been unblinded. The institution is responsible for providing continued follow-up (for patients who have been unblinded) on the same schedule as indicated in the study protocol for patients who have not been unblinded.

## 9.3 Bisphosphonate therapy

Choice of bisphosphonate therapy is at the physician's discretion within the parameters outlined in Sections 7.2.2 and 8.3. Bisphosphonate therapy dose must be the dose recommended for bone protection, not the dose recommended for anti-cancer therapy.

Bisphosphonate therapy must be obtained from commercial sources. Please refer to the current FDA-approved package insert provided with the medication or the *Physicians' Desk Reference* for information about possible side effects and storage.

*05/30/07* 10.0 **ADVERSE EVENT REPORTING REQUIREMENTS**

Please refer to Coordinator Online in the Members' Area of the NSABP Web site for general information regarding adverse event reporting.

10.1 **B-42 definitions for adverse event reporting**

*02/04/10*

10.1.1 ***Investigational agent***

The investigational agent administered in this protocol is letrozole/placebo. Letrozole is being used in this study under an IND sponsored by the NSABP. In this protocol, prior experience (expectedness) of adverse events for letrozole/placebo is based on the drug package insert for letrozole.

10.1.2 ***Commercial agent***

There are no commercial agents in B-42.

*02/04/10*

10.1.3 ***Double-blinded study drug***

This is a double-blinded study comparing letrozole to placebo. When an AE occurs that is expected for letrozole, the AE should be considered expected for the blinded study therapy. Conversely, when an AE occurs that is not listed for letrozole, the AE should be considered to be unexpected for the blinded therapy.

*12/07/10*

10.2 **Adverse event characteristics**

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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*04/16/14*

10.3 **Expedited reporting of adverse events**

NRG Oncology follows procedures for centralized reporting of serious adverse events. These adverse events are to be reported to NRG Oncology. NRG Oncology forwards reports and documentation to the appropriate regulatory agencies and the pharmaceutical company involved in the trial.

NRG Oncology is identified in the CTEP Adverse Event Reporting System (CTEP-AERS) as the Lead Group for NRG Oncology protocols which require CTEP-AERS reporting. A CTEP-AERS report must be submitted to the NRG Oncology Lead Group using the electronic web-based application located at https://eapps-ctep.nci.nih.gov/ctepaers. When initiating a CTEP-AERS report, the reporter will be directed to refer to the protocol for expedited reporting requirements. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NRG Oncology by telephone at: 412-624-2666. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

*04/16/14*

10.3.1 ***Expedited reporting methods***

- **CTEP-AERS-24 Notification:** requires that a CTEP-AERS 24-hour notification is electronically submitted to the NRG Oncology Lead Group within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification is followed by a complete CTEP-AERS report within 5 calendar days of learning of the event.

- **CTEP-AERS 5 Calendar Day Report:** requires that a CTEP-AERS report is electronically submitted to the NRG Oncology Lead Group within 5 calendar days of learning of the adverse event.

- **Supporting documentation** is required for all expedited (CTEP-AERS) reports. Include the protocol number, patient's study number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology SDMC (412-622-2113).

10.3.2 ***Expedited reporting requirements for investigational agents:***

- For patients who have been randomized and have received at least one dose of letrozole/placebo (investigational agent), follow the expedited reporting requirements as outlined in Table 3.

- Expedited adverse event reporting is *not required* for secondary cancers.

TABLE 3. CTEP-AERS expedited reporting requirements for adverse events that occur **within 6 months of the last dose** of the investigational agent (letrozole/placebo) *02/04/10, 12/07/10, 04/16/14*

| **Attribution** | **Grade 2** | **Grade 3** | | **Grade 4[b]** | | **Grade 5[a,b]** | | **Protocol-Specific Requirements/ Exceptions** |
|---|---|---|---|---|---|---|---|---|
| | *Unexpected* | *Unexpected* | *Expected* | *Unexpected* | *Expected* | *Unexpected* | *Expected* | |
| *Unrelated or Unlikely* | | | | CTEP-AERS | CTEP-AERS | CTEP-AERS | CTEP-AERS | -See footnote **(c)** for other requirements<br>-See footnote **(d)** for special ***requirements***<br>-See footnote **(e)** for special ***exceptions*** |
| *Possible, Probable, Definite* | | CTEP-AERS if hospitalized | | CTEP-AERS-24 and CTEP-AERS | | CTEP-AERS-24 and CTEP-AERS | | |

**CTEP-AERS-24:** Indicates a CTEP-AERS 24-hour notification must be electronically submitted to the NRG Oncology Lead Group *within 24 hours* of learning of the event.

**CTEP-AERS:** Indicates a complete expedited report must be electronically submitted to the NRG Oncology Lead Group *within 5 calendar days* of learning of the event.

**Hospitalization:** Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).

**All Reports:** On all reports, use the NCI protocol number, CTEP-AERS ticket number, and the protocol-specific patient ID provided during trial registration. ***Fax supporting documentation to the NRG Oncology SDMC.***

**a** All deaths within 6 months after the last dose of the investigational agent require expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. **Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a complete CTEP-AERS report is required as outlined in the table.**

**b** Adverse events that occur greater than 6 months after the last dose of the investigational agent with attribution of possible, probable or definite to the investigational agent require reporting as follows:

- CTEP-AERS 24-hour notification followed by a complete CTEP-AERS report within 5 calendar days of learning of the event for:
  - grade 4 unexpected events
  - grade 5 unexpected events
- CTEP-AERS 5-calendar day report for:
  - grade 5 expected events

**c** 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.

**d Protocol-specific expedited reporting requirements:** For B-42 the CTEP-AERS reporting requirements are extended to 6 months after the last dose of the investigational agent (letrozole/placebo) to facilitate data collection.

- ***From the first dose of study therapy, the following require expedited reporting via CTEP-AERS (see Sections 10.4 and 10.9):***
  - Leukemia secondary to oncology chemotherapy (arising as a result of the mutagenic effect of chemotherapy agents);
  - Myelodysplastic syndrome;
  - Treatment-related secondary malignancy (only if development was ***most probably*** as a result of treatment for previously existing malignancy).

**e Protocol-specific expedited reporting exceptions:** For this study, the adverse events listed below which occur, including hospitalizations for these events, do **not** require expedited reporting via CTEP-AERS:

- Neoplasms-malignant (i.e., a second primary malignancy) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy. (See footnote **d** and Section 10.9.)

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*04/16/14*

## 10.4 Reporting a secondary malignancy

A ***secondary malignancy*** is a cancer caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur on NCI-sponsored trials either during or following treatment must be reported via CTEP-AERS within 5 days of learning of the secondary malignancy. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Supporting documentation, including pathology and cytogenetics reports which confirm the secondary malignancy, must be faxed to the NRG Oncology SDMC expedited fax at 412-622-2113. Each page of supporting documentation must include the NCI protocol number, the CTEP-AERS ticket number, and the protocol-specific Patient ID number provided during trial registration.

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in the B-42 protocol (see Section 10.9).

*04/16/14*

### 10.4.1 *Second malignancy*

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting online on the B-42 Form F (see Section 10.9).

## 10.5 Expedited reporting of pregnancy, fetal death, and death neonatal occurring during study therapy

Any pregnancy, fetal death, or death neonatal occurring while the patient is receiving study therapy or within 6 months following the last dose of study therapy must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

Upon learning of a pregnancy, fetal death, or death neonatal that occurs during study or within 6 months following the last dose of study therapy the investigator is required to:

- Call the Clinical Coordinating Department (see Information Resources**).** ***Patients must immediately discontinue receiving study therapy.***
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6):
  - Create and submit an CTEP-AERS report;
  - Complete the Pregnancy Information Form (located in the NSABP Members' Area in Protocol B-42 "Forms and Supporting Documents"); and

- Fax the completed Pregnancy Information Form with all available supporting documentation to the NRG Oncology SDMC's expedited fax number at 412-622-2113.

- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Information Form used for the initial report.

- For questions concerning AE reporting, contact the AE Reporting Nurse (see Information Resources**)**.

## 10.6 Other recipients of expedited adverse event reports

- NRG Oncology will forward reports and documentation to the appropriate regulatory agencies and the pharmaceutical company involved in this trial.

- Adverse events determined to require expedited reporting must also be reported by the investigator to the Institutional Review Board responsible for safety oversight of the patient according to the local policy and procedures.

## 10.7 Routine reporting of adverse events

### 10.7.1 *Online reporting on the B-42 Adverse Event Form*

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- Adverse events are to be assessed every 6 months during study therapy and 6 months after the last administered dose of the investigational agent (letrozole/placebo).
- Direct online entry of adverse events is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site.
- **All grade 3 adverse events not reported via CTEP-AERS** (see Table 3 for expedited reporting requirements) are to be reported online on the Adverse Event Form.
- The following protocol-specific **grade 2** adverse events *(and **grade 1** adverse events as noted in parentheses)* must be reported online on the Adverse Event Form:
  - Cardiac disorders
    - Acute coronary syndrome
  - Investigations
    - Cholesterol, high
  - Metabolism and nutrition disorders
    - Hypertriglyceridemia
  - Musculoskeletal and connective tissue disorder
    - Arthralgia
    - Myalgia
  - Nervous system disorders
    - Ischemia cerebrovascular
    - Stroke *(must also report grade 1)*
    - Transient ischemia attack *(must also report grade 1)*
  - Vascular disorders

- Peripheral ischemia
- Thromboembolic events
- Visceral arterial ischemia

- The following adverse events **are not reported** on the Adverse Event Form:
  - Adverse events that require expedited reporting (see Table 3)
  - Adverse events that occur after breast cancer recurrence
  - Neoplasms-malignant (i.e., a secondary primary) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy
- Supporting documentation for each adverse event reported online on the Adverse Event Form must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

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#### 10.7.2 *Submission of the B-42 Adverse Event Form*

- The Adverse Event Form is submitted online to the NRG Oncology SDMC as soon as possible after adverse events have been assessed every 6 months.
- The final Adverse Event Form is completed and submitted online to the NRG Oncology SDMC 6 months after the final dose of the investigational agent (letrozole/placebo).

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### 10.8 Reporting selected adverse events on the B-42 Follow-up Form

Note: Supporting documentation for the osteoporosis evaluation findings and for late thrombotic events reported online on the B-42 Follow-up Form must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

#### 10.8.1 *Thrombotic events*

**After the final Adverse Event Form is submitted**, the following adverse events ***must*** be reported online on the Follow-up Form:

- ≥ grade 1
  - stroke
  - transient ischemic attack
- ≥ grade 2
  - acute coronary syndrome
  - ischemia cerebrovascular
  - peripheral ischemia
  - thromboembolic events
  - visceral arterial ischemia

- ≥ grade 3
  - myocardial infarction

10.8.2 ***Osteoporosis evaluation findings***

**During therapy and throughout follow-up**, the following must be reported online on the Follow-up Form:

- Osteoporotic fractures
  - Wrist
  - Hip
  - Spine
- Bone mineral density T-scores

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## 10.9 Reporting second primary malignancies

Report all second primary malignancies (including leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, and treatment-related secondary malignancy previously reported through CTEP-AERS) on the online B-42 Follow-up Form. Fax supporting documentation that confirms the second primary cancer diagnosis with the transmittal form (provided by the online software and printed) to 412-622-2111.

## 11.0 DIAGNOSIS OF BREAST CANCER RECURRENCE AND OTHER EVENTS

- The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when both the clinical and laboratory findings meet "acceptable" criteria as defined below. Suspicious findings do not constitute criteria for breast cancer recurrence, nor are they an indication to alter protocol therapy.
- **PET scans may be performed at the discretion of the investigator; however PET scans, in the absence of objective findings on CT, MRI, or other imaging studies do not meet the criteria of an acceptable method of determining breast cancer recurrence for this study.** *Any recurrence of malignant disease should be proven by biopsy whenever possible.*
- Please submit a copy of the clinic/office note summarizing the work-up and treatment plan for a recurrence or a second primary cancer.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

*09/12/07*

### 11.1 Local recurrence

Recurrent tumor is defined as evidence of invasive or in situ breast cancer (except LCIS) in the ipsilateral breast or skin of the breast. Patients who develop clinical evidence of tumor recurrence in the ipsilateral breast must have a biopsy of the suspicious lesion to confirm the diagnosis.

- Acceptable: positive cytology or histologic biopsy

#### 11.1.1 *Ipsilateral breast tumor recurrence (IBTR)*

An IBTR event is defined as recurrent tumor in either the ipsilateral breast parenchyma or skin of the breast occurring after lumpectomy.

#### 11.1.2 *Other local recurrence*

Defined as recurrence in the skin of the chest wall (exclusive of the breast) or chest wall.

### 11.2 Regional recurrence

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, after operation.

- Acceptable: positive cytology or histologic biopsy

### 11.3 Distant recurrence

Defined as evidence of tumor in any area of the body, with the exception of those described in Sections 11.1 and 11.2.

11.3.1 ***Skin, subcutaneous tissue, and lymph node (other than local or regional) metastases***

- Acceptable: (i) positive cytology, histologic biopsy, or (ii) radiologic evidence of metastatic disease

11.3.2 ***Bone marrow metastasis***

- Acceptable: (i) positive cytology, histologic biopsy, or (ii) MRI scan

11.3.3 ***Lung metastasis***

- Acceptable: (i) positive cytology, histologic biopsy, or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases

NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations such as biopsy or needle aspiration must be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

11.3.4 ***Skeletal metastasis***

- Acceptable: (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis; or (ii) biopsy proof of bone metastases; or (iii) bone scan that is clearly positive for bone metastases

NOTE: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

11.3.5 ***Liver metastasis***

- Acceptable: (i) an abdominal CT scan, liver scan, ultrasound, or MRI consistent with liver metastases, or (ii) liver biopsy confirmation of the metastatic disease

NOTE: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

11.3.6 ***Central nervous system metastasis***

- Acceptable: (i) positive CT scan or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology (for a diagnosis of meningeal involvement)

### 11.4 Second primary breast cancer

Defined as evidence of invasive or in situ breast cancer (except LCIS) in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed histologically.

- Acceptable: positive histologic biopsy

### 11.5 Second primary cancer (non-breast)

Any non-breast second primary cancer other than squamous and basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the colon and cervix will be considered an event in the analysis of DFS. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

*12/07/10*

### 11.6 Arterial thrombotic events

The following CTCAE v4.0 arterial thrombotic events will be considered an event in the analysis of the secondary endpoints:

- ≥ grade 1
  - stroke
  - transient ischemic attack
- ≥ grade 2
  - acute coronary syndrome
  - ischemia cerebrovascular
- ≥ grade 3
  - myocardial infarction
  - peripheral ischemia
  - visceral arterial ischemia
- ≥ grade 4
  - selected thromboembolic events (cerebrovascular event, arterial insufficiency)

### 11.7 Osteoporotic-related fractures

Any osteoporotic-related wrist, hip, or spine fracture will be considered an event in the analysis of secondary endpoints.

*04/16/14*

### 11.8 Documentation required following death

- Autopsy reports must be secured whenever possible and submitted to the NRG Oncology SDMC.
- A copy of the death certificate must be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Submit the last clinic/office note made before the death or the physician's note summarizing events resulting in death.

## 12.0 PATIENT ENTRY AND WITHDRAWAL PROCEDURES

*02/04/10* *Note: Accrual closed on January 6, 2010, following achievement of the sample size goal.*

### 12.1 Patient consent form

Before the patient is enrolled, the consent form (see Appendix D), including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

*01/23/09*

### 12.2 Entry

*At the time of Amendment #3, the Oncology Patient Enrollment Network (OPEN) was implemented. NSABP investigators should refer to Patient Entry Guidelines in the Members' Area of the NSABP Web site; CTSU investigators should refer to Appendix B.*

#### 12.2.1 *NSABP Investigators*

*Note: NSABP investigators who also are registered with the CTSU must enroll B-42 patients through the NSABP; they are not permitted to enter patients through the CTSU.*

**Patient entry instructions can be found in the "Patient Entry Guidelines" section of the Members' Area of the NSABP Web site,** https://members.nsabp.pitt.edu.

#### 12.2.2 *CTSU Investigators*

CTSU investigators must follow procedures outlined in Appendix B, Section 1.0, *Site Registration and Patient Entry for CTSU Investigators.*

### 12.3 Patient study number

After all of the eligibility criteria have been met, the institution will receive the patient's nine-digit study number.

### 12.4 Patient-initiated discontinuation of study drug

Even after a patient agrees to take part in this study, she may stop study drug or withdraw from the study at any time. If study drug is stopped but she still allows the study doctor to submit information, study data and other materials must be submitted according to the study schedule.

*04/16/14*

### 12.5 Withdrawal from the study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology SDMC), the investigator must provide the NRG Oncology SDMC with written documentation of the patient's decision to fully withdraw from the study.

### 12.6 Investigator-initiated discontinuation of study drug

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study drug if one of the following occurs:

- the patient develops a serious side effect that she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drugs or other treatments for breast cancer becomes available.

## 13.0 REQUIRED FORMS AND MATERIALS

### 13.1 Data collection

B-42 data collection will include the following elements:

- Characteristics of the breast cancer
- Cardiac risk factors
- Start date and end date of study drug
- Estimate of study drug compliance
- Adverse events every 6 months during study therapy and 6 months after the last dose of study drug
- Bisphosphonate use (including agent and dose)
- Lipid therapy
- Breast cancer events (local, regional, and distant)
- Second primary cancer events
- Survival
- Osteoporotic bone fractures
- Arterial thrombotic events

### 13.2 Instructions for completion and submission of B-42 forms and materials

- For B-42, data will be submitted by direct online entry through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site.

- B-42 data form worksheets and specimen transmittal forms, as well as instructions for completion and submission of B-42 data and materials, are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu. (CTSU investigators should refer to Appendix B and the NSABP B-42 Web page located on the CTSU Registered Member site.)

- See Section 6.0 for tissue submission requirements and submission instructions.

## 14.0 STATISTICAL CONSIDERATIONS

### 14.1 Randomization and treatment assignments

Participants will be randomized in a double-blind fashion. The stratification factors will be pathologic nodal status (negative or positive), tamoxifen as adjuvant therapy (yes or no), and lowest bone mineral density T score for LS spine, total hip, or femoral neck (> -2.0 or ≤ -2.0 SD). In order to avoid extreme inequality in treatment assignment within an institution, an adaptive randomization scheme which incorporates a biased-coin approach will be employed.[45,46]

### 14.2 Primary endpoint

The primary endpoint for analysis is disease-free survival (DFS). DFS endpoints are local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (IBTR), regional recurrence, distant recurrence, second primary cancer (other than squamous and basal cell carcinoma of the skin, melanoma in situ, and carcinoma in situ of the colon and cervix), and death from any cause prior to recurrence or second primary cancer.

*12/07/10*

### 14.3 Secondary endpoints

Secondary endpoints are survival (S), breast cancer free interval, distant recurrence, arterial thrombotic events, and osteoporotic-related fractures (Colles', hip and spine). The S endpoint is defined as death from any cause. The breast cancer-free interval endpoint is defined in this study to be the time from randomization to recurrence or contralateral second primary breast cancer. Other second primary cancers and death without evidence of recurrent disease will be treated as censored events in this case. The distant recurrence endpoint is defined in this study to be the time of randomization to distant recurrence of breast cancer. The osteoporotic-related fractures endpoint is defined in this study to be Colles', hip, and spine. The arterial thrombotic events endpoint is defined in this study as the incidence of ≥ grade 1 stroke, transient ischemic attack; ≥ grade 2 acute coronary syndrome, ischemia cerebrovascular; ≥ grade 3 myocardial infarction, peripheral ischemia, visceral arterial ischemia; and ≥ grade 4 selected thromboembolic events (cerebrovascular event, arterial insufficiency). All endpoints (DFS, S, breast cancer-free interval, distant recurrence, arterial thrombotic events, and fractures) will be measured from the date of randomization following 5 years of treatment with an AI or the combination of tamoxifen and an AI.

### 14.4 Statistical analysis

Differences in the primary and secondary endpoints between the placebo arm and letrozole arms will be assessed by the stratified log-rank tests, controlling for the variables used for stratification of randomization. Two-sided tests will be used with control of type I error rate at the 0.05 level.

In secondary analyses, the proportional hazards model[47] will be used to estimate and to control for the effect of additional prognostic variables such as clinical tumor size and ER level. Wald tests will be used to assess the prognostic importance of each variable, and treatment-by-covariate interactions will be tested by adding interaction terms one at a time to the models. The sample size specified above may be inadequate to support detailed subgroup analyses. Such subgroup analyses will be carried out only in the event that preliminary tests of treatment-by-group interactions are strongly significant ($p < 0.01$).

Definitive analysis will be based on the intent-to-treat principle, with all patients analyzed as randomized, regardless of eligibility or protocol compliance. An eligibles-only analysis will be also completed, and any substantive discrepancies between the results of this analysis and the intent-to-treat analysis will be fully investigated.

### 14.5 Interim analyses of outcome

Four interim analyses are scheduled prior to the definitive analysis: after 126, 252, 379, and 505 events. Symmetric stopping boundaries will be employed based on the O'Brien-Harrington-Fleming method.[48] Two-sided boundaries correspond to z-scores of |4.56|, |3.23|, |2.63|, and |2.28|, respectively. Under our data management system, summary data files are locked based on the last day of the month each quarter. Therefore, the numbers of events observed in the data file used at each particular interim analysis may be slightly higher than the values given above. If significant deviations from the defined values occur, the nominal levels of significance will be adjusted by alpha-spending.[49]

### 14.6 Sample size considerations

We reviewed data from the NSABP Protocols B-20 (excluding the tamoxifen-only arm) and B-23 to estimate the annual hazard rate (corresponding to DFS) for node-negative patients. Similarly, we reviewed data from the NSABP Protocol B-28 to estimate the annual hazard rate for node-positive patients. We considered only women who remained disease free after 5 years of treatment with combination of a chemotherapy and tamoxifen assuming that the annual hazard rate in the population for the present study would have a similar pattern. For node-negative patients, the estimated hazard rate (conditioning on having been disease free through 5 years) was 0.025. For node-positive patients, the estimated hazard rate was 0.051.

Assuming 50% of the patients accrued to this protocol will be node-negative and 50% will be node-positive, the expected overall hazard estimate (corresponding to DFS) would be approximately 0.038 for the control group. This corresponds to an 82.7% absolute 5-year DFS for the control arm.

We designed the study to be able to detect a 20% reduction in the annual hazard rate in DFS with a power of 80%, using a two-sided 0.05-level log-rank test. This requires that the number of DFS events be 631. Thus, if we accrue 3,840 patients in 5.25 years and include a non-compliance rate of 4% per year, we should reach this number of events approximately 3.95 years after the closure of accrual, i.e., 9.2 years after the initiation of the study (see Table 4).

TABLE 4. Anticipated accrual pattern

| Years of Study | Years of Registration | Years of Accrual | # of Women Registered With < 5 Years of Therapy | # of Women Randomized After 5 years of Initial Therapy | Time Summary |
|---|---|---|---|---|---|
| 1 | 1 | 1 | 1,440 | 240 | Up to 5 Years of Registration<br><br>5.25 Years of Accrual<br><br>3.95 Years of Follow-up After Accrual |
| 2 | 2 | 2 | 1,440 | 480 | |
| 3 | 3 | 3 | 1,440 | 960 | |
| 4 | 4 | 4 | 1,440 (tentative)* | 960 | |
| 5 | 5 | 5 | 1,440 (tentative)* | 960 | |
| 6 | --- | 6 | --- | 240 | |
| 7 | --- | --- | --- | --- | |
| 8 | --- | --- | --- | --- | |
| 9 | --- | --- | --- | --- | |
| Total Women | | | 7,200 | 3,840 | 9.2 Years |

* Registration in years 4 and 5 is tentative depending on the rate of patient registration, average time on drug when registered, and proportion registered in the first three years that go on to be randomized.

### 14.7 **Accrual rates**

Based on the accrual rates from NSABP Protocols B-20 (node-negative), B-23 (node-negative), and B-28 (node-positive), we expect that the registration rate would be 120 patients per month, i.e., 1,440 patients annually. Also, assuming that only two-thirds of the remaining disease-free patients would be interested in participating in the study, it is expected that the accrual rate would be 20 per month for the first year, 40 per month for the second year, and 80 patients per month for the remaining 3.25 years (see Table 4).

### 14.8 **Monitoring of adverse events and institutional performance**

The occurrence of adverse events, including toxicities, second primary cancers, and deaths, will be continuously monitored. Summaries of all adverse events will be prepared and discussed at monthly meetings of the Medical Affairs Committee.

Throughout the period in which the protocol is open to accrual or patients are receiving therapy, progress reports will be made to the DMC at 6-month intervals. These reports will include an assessment of toxicities, second primary cancers, and on-study deaths; a comparison of actual and projected accrual; and an assessment of data quality, including data delinquency and rates of eligibility. After accrual is closed, reports of adverse events together with the results of planned interim analyses of S and DFS will be presented to the DMC.

## 14.9 Issues relating to racial and ethnic differences

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians.[50,51] This difference has been attributed to many factors, including more advanced disease at the time of diagnosis,[52] social and economic factors,[53] or specific tumor characteristics such as ER positivity.[54, 55] Although outcomes tend to be less favorable for African American, significant race-by-treatment interactions have not been previously reported, suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.[56, 57]

Potential for the enrollment of minority patients in this protocol is enhanced by the NSABP's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NSABP investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distribution of ethnicity for the present study is projected from the NSABP B-33 study, which had already accrued 1,598 patients even though it was terminated early. The NSABP B-33 study population consisted of 90% white; 4% black, not of Hispanic origin; 6% other, including 3% of Hispanic and 2% of Asian or Pacific Islander descent. The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

TABLE 5. Expected racial and ethnic composition of NSABP B-42

| Ethnic Category | Total |
|---|---|
| Hispanic or Latino | 115 |
| Not Hispanic or Latino | 3,725 |
| **Ethnic Category: Total of all subjects** | 3,840 |
| **Racial Category** | |
| American Indian or Alaskan Native | 38 |
| Asian | 58 |
| Black or African American | 154 |
| Native Hawaiian or other Pacific Islander | 19 |
| White | 3,571 |
| **Racial Category: Total of all subjects** | 3,840 |

| | |
|---|---|
| **Ethnic Categories:** | **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. |
| | **Not Hispanic or Latino** |
| **Racial Categories:** | **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment. |
| | **Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. |
| | **Black or African American** – a person having origins in any of the black racial Groups of Africa. |
| | **Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. |
| | **White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. |

## 15.0 PUBLICATIONS INFORMATION AND ADMINISTRATIVE AGREEMENTS

The publication or citation of study results will be made in accordance with the publication policy of the NRG Oncology that is in effect at the time the information is to be made publicly available.

## 16.0 **REFERENCES**


1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998; 351:1451-1467.

2. Baum M, Brinkley DM, Dossett JA, et al. Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer. 'Nolvadex' Adjuvant Trial Organisation. Br J Cancer 1988; 57:608-611.

3. Bartlett K, Eremin O, Hutcheon A, et al. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. Lancet 1987; 2:171-175.

4. Ribeiro G, Swindell R. The Christie hospital adjuvant tamoxifen trial--status at 10 years. Br J Cancer 1988; 57:601-603.

5. Cancer Research Campaign Group. The effect of adjuvant tamoxifen: the latest results from the Cancer Research Campaign Adjuvant Breast Trial. Cancer Research Campaign Breast Cancer Trials Group. Eur J Cancer 1992; 28A:904-907.

6. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989; 320:479-484.

7. Swedish Breast Cancer Cooperative Group. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. Swedish Breast Cancer Cooperative Group. J Natl Cancer Inst 1996; 88:1543-1549.

8. Current Trials Working Party on the Cancer Research Campaign Breast Trials Group. Preliminary results from the cancer research campaign trial evaluating tamoxifen duration in women aged fifty years or older with breast cancer. Current Trials working Party of the Cancer Research Campaign Breast Cancer Trials Group. J Natl Cancer Inst 1996; 88:1834-1839.

9. Fisher B, Brown A, Wolmark N, et al. Prolonging tamoxifen therapy for primary breast cancer. Findings from the National Surgical Adjuvant Breast and Bowel Project clinical trial. Ann Intern Med 1987; 106:649-654.

10. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol 1996; 14:2000-2011.

11. Jonat W, Howell A, Blomqvist C, et al. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. Eur J Cancer 1996; 32A:404-412.

12. Buzdar AU, Jones SE, Vogel CL, et al. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. Cancer 1997; 79:730-739.

13. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 1998; 83:1142-1152.

14. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 1998; 16:453-461.

15. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001; 19:3357-3366.

16. Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. J Clin Oncol 2000; 18:1399-1411.

17. Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000; 18:3748-3757.

18. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000; 18:3758-3767.

19. Bonneterre J, Buzdar A, Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Cancer 2001; 92:2247-2258.

20. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001; 19:2596-2606.

21. Paridaens R, Dirix L, Beex L. Exemestane (Aromasin) is active and well tolerated as first-line hormonal therapy (HT) of metastatic breast cancer (MBC) patients (pts): results of a randomized phase II trial. Proc Am Soc Clin Oncol 2000; 19:83a: Abstr 316.

22. Paridaens R, Therasse P, Dirix L, et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) - A randomized phase III trial of EORTC Breast Group. Proc Am Soc Clin Oncol 2004; 23:6 Abstr 515.

23. Baum M, Buzdar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002; 359:2131-2139.

24. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003; 98:1802-1810.

25. Thuerlimann B, Senn HJ. For the BIG 1-98 collaborative: Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer: first results of IBCSG 18-98/BIG 1-98. St. Gallen consensus conference, 2005.

26. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350:1081-1092.

27. Jakesz R, Kaufmann M, Gnant M, et al. Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial. Br Ca Res Treat 2004; 88:s7 Abstr 2.

28. Boccardo F, Rubagotti A, Amoroso D, et al. Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. Br Ca Res Treat 2003; 82:S6, Abstr 3.

29. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349:1793-1802.

30. Peto R. Five years of tamoxifen--or more? J Natl Cancer Inst 1996; 88:1791-1793.

31. Early Breast Cancer Trialists Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992; 339:71-85.

32. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 1996; 88:1529-1542.

33. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 2001; 93:684-690.

34. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. J Natl Cancer Inst 2001; 93:456-462.

35. Jakesz R, Samonigg H, Greil R, et al. Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). Proc Am Soc Clin Oncol 2005; Abstr 527.

36. Goss, PE. Personal communication, 2005.

37. Howell A, on behalf of the ATAC Trialists' Group A. University of Manchester, Manchester, United Kingdom. ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen. Br Ca Res Treat 2004; 88:s7 Abstr 1.

38. Howell A. Adjuvant aromatase inhibitors for breast cancer. Lancet 2005; 366 (9484):431-433.

39. Thurlimann BJ, Keshaviah A, Mouridsen H, et al. BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Proc Am Clin Oncol 2005; Abstr 511.

40. Boccardo FM, Rubagotti A, Puntoni M, et al. Switching to anastrozole (ANA) vs. continued tamoxifen (TAM) treatment of early breast cancer (EBC): Updated results of the Italian tamoxifen anastrozole (ITA) trial. Proc Am Clin Oncol 2005; Abstr 526.

41. Coombes RC, Hall E, Snowdon CF, et al. The Intergroup Exemestane Study: a randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen-updated survival analysis. Br Ca Res Treat 2004; 88:s7 Abstr 3.

42. Dowsett M, Cuzick J, Wale C, et al. Retrospective Analysis of Time to recurrence in the ATAC Trial According to Hormone Receptor Status: An Hypothesis-Generating Study. J Clin Oncol 2005 Oct 20; 23(30):7512-7517.

43. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23(22):5108-5116.

44. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy that tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001; 19(18):3808-3816.

45. White SJ, Freedman LA. Allocation of patients to treatment groups in a controlled clinical trial. Br J Cancer 1978; 37:849-857.

46. Efron B. Forcing a sequential experiment to be balanced. Biometrika 1971; 58:403-417.

47. Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Society, Series B 1972; 34:187-220.

48. Fleming TR, Harrington DP, O'Brien PC: Designs for group sequential tests. Controlled Clinical Trials 1984; 5:348-361.

49. Lan KG, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70:659-663.

50. Baquet CR, Ringen K, Pollack ES, et al. Cancer Among Blacks and Other Minorities: Statistical Profiles. Bethesda MD: National Institutes of Health. DHEW publication (NIH), 1986; 86:2785.

51. Young JL Jr, Ries LG, Pollack ES. Cancer patient survival among ethnic groups in the United States. J Natl Cancer Inst 1984; 73:341-352.

52. Satariano WA, Belle SH, Swanson GM. The severity of breast cancer at diagnosis: A comparison of age and extent of disease in black and white women. Am J Public Health 1986; 76:779-782.

53. Bassett MT, Krieger N. Social class and black-white differences in breast cancer survival. Am J Public Health 1986; 76:1400-1403.

54. Crowe JP Jr, Gordon NH, Hubay CA, et al. The interaction of estrogen receptor status and race in predicating prognosis for stage I breast cancer patients. Surgery 1986; 100:599-605.

55. Mohla S, Sampson CC, Khan T, et al. Estrogen and progesterone receptors in breast cancer in black Americans: Correlation of receptor data with tumor differentiation. Cancer 1982; 50:552-559.

56. Dignam JJ, Redmond CK, Fisher B, et al. Prognosis among African-American women and white women with lymph node-negative breast carcinoma: Findings from two randomized clinical trials of the National Surgical Adjuvant Breast and Bowel Project (NSABP). Cancer 1997; 80:80-90.

57. Costantino JP, Redmond CK, Wickerham D, et al. A comparison of survival between white and black breast cancer patients: Results from NSABP B-09. Proc Am Soc Clin Oncol 1987; 6:230 Abstr 905.

**APPENDIX A**
**OPTIONAL B-42 LETROZOLE REGISTRATION PROGRAM**

*Note: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment. As of January 6, 2010, the NSABP B-42 randomized treatment trial closed to patient accrual following achievement of the sample size goal. Data collection for the NSABP B-42 randomized treatment trial continues as planned.*

## 1.0 Introduction

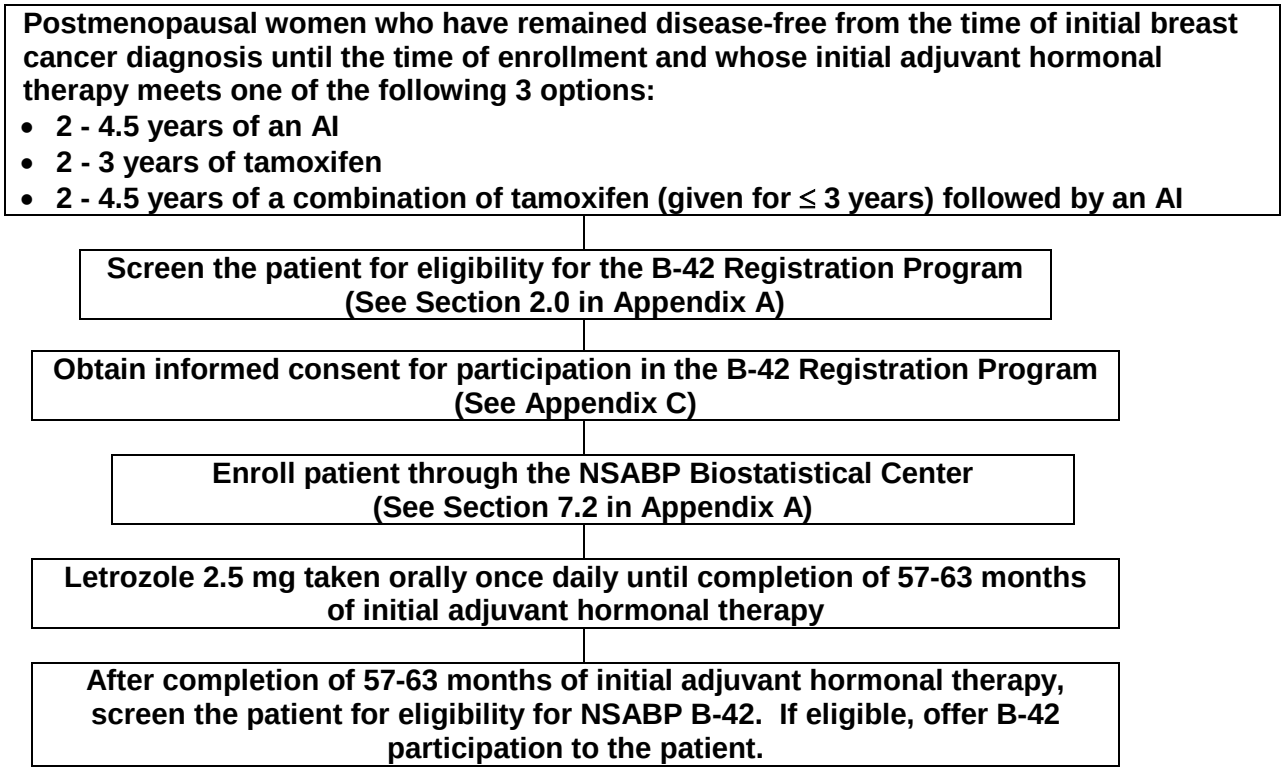
In order to have a predominantly letrozole-treated population for enrollment in the randomized B-42 trial, patients who have had a minimum of 2 years of hormonal therapy and who are currently taking tamoxifen (for up to 3 years) or an AI may be offered letrozole at no cost until they complete 5 total years of hormonal therapy. These patients should then be offered participation in B-42.

The number of patients registered to receive letrozole on the Letrozole Registration Program, along with time on hormonal therapy at registration, will be monitored by the NSABP to guide decisions regarding closure of the Letrozole Registration Program. It is anticipated that between 5,640 and 7,200 patients will be needed for the Letrozole Registration Program.

***Appendix A provides instructions for enrolling patients into the optional B-42 Registration Program. Instructions in the protocol for the B-42 randomized study do not apply to the Registration Program.***

Figure A1

**OPTIONAL B-42 LETROZOLE REGISTRATION PROGRAM OVERVIEW**



## 2.0 PATIENT ELIGIBILITY/INELIGIBILITY CRITERIA

### 2.1 Patient selection guidelines

*The guidelines in Section 2.1 of Appendix A will **not** be considered exclusion criteria for receiving letrozole through the optional B-42 letrozole Registration Program; however, in addition to the formal eligibility/ineligibility criteria in Sections 2.2 and 2.3, investigators should consider each of these factors when selecting patients for the Registration Program. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the therapy when deciding if a patient is appropriate for this program. These considerations should be weighed carefully, as they may make a patient an unsuitable candidate for the B-42 Registration Program (and for possible participation in the B-42 randomized study) and may increase risk to the patient:*

- Patients with a life expectancy less than 10 years, excluding her diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)

- Patients who have demonstrated unacceptable compliance with previous tamoxifen and AI or AI therapy. *(Note: Patients may have had drug holidays, as long as the frequency or duration of the drug holidays does not indicate to the investigator that the patient will not be compliant with taking letrozole to complete 5 years of initial adjuvant hormonal therapy.)*

- Patients for whom bisphosphonate therapy is not recommended or not tolerated. *(Note: Bisphosphonate therapy is a recommended intervention in the osteoporosis management instructions in the Registration Program and the B-42 randomized study.)*

- Patients with a documented history of hypercholesterolemia that is not responsive to cholesterol-lowering therapy.

- Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

### 2.2 Conditions for patient eligibility

Patients who satisfy all of the following conditions are the only patients who will be considered eligible to receive letrozole through the B-42 Registration Program.

2.2.1 The patient must have consented to participate, must have signed and dated an appropriate IRB-approved consent form for the Registration Program (see Appendix C) that conforms to federal and institutional guidelines.

2.2.2 Patients must be female.

2.2.3 Patients must be postmenopausal at the time of enrollment (Note: Premenopausal or perimenopausal women requiring therapy with luteinizing hormone-releasing hormone [LHRH] analogs to suppress ovarian function are not eligible.)

For study purposes, postmenopausal is defined as:

- age 56 or older with no spontaneous menses for at least 12 months prior to study entry, **or**
- age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) AND with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standards, **or**
- a prior documented bilateral oophorectomy.

2.2.4 The patient must have remained disease-free from the time of initial breast cancer diagnosis until the time of enrollment in the Registration Program.

2.2.5 The patient must have had histologically-confirmed invasive carcinoma of the breast by diagnostic core needle biopsy or by final pathologic evaluation of the surgical specimen.

2.2.6 Patients who received neoadjuvant chemotherapy must have been clinical Stage I, II, or IIIA. For patients who received adjuvant chemotherapy, the primary tumor must have been T1-3 on pathologic evaluation and ipsilateral nodes must have been pN0, pN1 ($pN1_{mi}$, $pN1_a$, $pN1_b$, $pN1_c$), $pN2_a$, $pN3_a$, or $pN3_b$. Refer to the Members' Area of the NSABP Web site for TNM nomenclature and staging information.

2.2.7 The primary tumor must have been ER-positive and/or PgR-positive. (Patients who had tumors that were considered to be borderline for hormone receptor positivity and who were treated with tamoxifen and/or an aromatase inhibitor [AI] are eligible.)

2.2.8 Patients must have undergone either a lumpectomy with axillary nodal staging (followed by breast radiotherapy) or a total mastectomy and axillary nodal staging. (Acceptable axillary nodal staging procedures include sentinel node biopsy alone, if sentinel nodes were negative on H&E staining.)

2.2.9 The patient must be currently taking an aromatase inhibitor (AI) or tamoxifen.

2.2.10 The patient must have received a duration of a minimum of 2 years but not more than 4.5 years (regardless of missed doses) of initial adjuvant hormonal therapy. Total duration of tamoxifen must not exceed 3 years.

### 2.3 Conditions for patient ineligibility

Patients with one or more of the following conditions will be ineligible:

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2.3.1 Diagnosis of bilateral breast cancer including DCIS (synchronous or metachronous).

2.3.2 History of non-traumatic osteoporotic fracture of wrist, hip, or spine.

2.3.3 Other malignancies unless the patient is considered to be disease-free for 5 or more years prior to enrollment, and is deemed by their physician to be at low risk for recurrence. Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: carcinoma in situ of the cervix, colon carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.

2.3.4 Any sex hormonal therapy, e.g., estrogen- or progesterone-replacement therapy or oral contraceptives. These patients are eligible only if this therapy is discontinued prior to enrollment. (See Section 4.3 of Appendix A for exceptions.)

2.3.5 Therapy with any hormonal agent such as raloxifene for management of osteoporosis. (Patients are eligible only if these medications are discontinued prior to enrollment.)

2.3.6 Current treatment with any other investigational hormonal therapy or current participation in any other hormonal therapy clinical trial.

## 3.0 REQUIRED STUDIES

Testing and exams are at the investigator's discretion during the B-42 Registration Program.

## 4.0 TREATMENT

### 4.1 Letrozole instructions

Letrozole 2.5 mg tablet will be taken orally once daily to complete 5 years of initial adjuvant hormonal therapy. Letrozole may be taken without regard to meals. Refer to the package insert for detailed letrozole description and other information.

Letrozole should begin as soon as possible following enrollment in the Registration Program. Letrozole is to be given continuously until the patient has reached 5 years of initial adjuvant hormonal therapy. The patient will then be eligible for enrollment in the B-42 randomized study, *if all other B-42 eligibility criteria are met at that time*.

If the patient chooses not to enroll in the B-42 randomized study, letrozole (provided through the Registration Program) must end 5 years from the date of the ***first dose of adjuvant hormonal therapy (either tamoxifen or AI)*** regardless of any missed doses.

### 4.2 Osteoporosis management

***All patients should be evaluated clinically for osteoporosis and fracture risks. For detailed information regarding major risk factors for osteoporosis and related fractures, refer to the National Osteoporosis Foundation (NOF) Web site at http://www.nof.org.***

4.2.1 Annual bone mineral density (BMD) testing during therapy with any AI is strongly recommended for all patients; timing is at the investigator's discretion during the Registration Program. ***The American Society of Clinical Oncology's bisphosphonate guidelines identifies postmenopausal patients taking an AI as being at high risk for osteoporosis and recommends annual BMD testing.*** (Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003; 21:4042-4057.)

4.2.2 Osteoporosis ***management*** recommendations

The osteoporosis management interventions are ***strongly recommended for all B-42 Registration Program participants***.

- Calcium supplement 500-600 mg po given BID is recommended for all patients.
- Vitamin D 800-1000 IU po once daily is recommended for all patients.
- Bisphosphonate therapy is recommended for women who meet any of the criteria below:
  - T score of -2.0 SD or less
  - Risk factors for bone fracture (refer to the NOF Web site) and T score of -1.5 SD or less
  - Osteoporotic wrist, spine or hip fracture (after Registration Program enrollment)

  ***Specific agent is at investigator's discretion. Bisphosphonate therapy dose must be the dose recommended for bone protection, not the dose recommended for anti-cancer therapy.***
- Additional interventions recommended for all patients include weight-bearing exercise and resistance exercise.

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4.3 **Postmenopausal hormonal therapy**

- Non-hormonal therapy interventions (e.g., Astroglide® or Replens®), *instead of hormonal therapy*, are strongly encouraged for management of postmenopausal vaginal symptoms. *Although the use of topical vaginal hormonal therapies is not encouraged*, at the investigator's discretion, conjugated estrogen ring (Estring®) is permitted.
- Patients may ***not*** receive any of the following types of hormonal therapy:
  - Selective estrogen receptor modulators (SERMs) for example raloxifene (Evista®).
  - Sex hormonal therapy, e.g., estrogen- or progesterone-replacement therapy (including low-dose estrogen in the form of vaginal cream) and oral contraceptives.
  - Femring®.
  - Vagifem®.
  - Luteinizing hormone-releasing hormone (LHRH) agonist/antagonists (e.g., Zoladex®).
  - Aromatase inhibitors.

## 5.0 ADVERSE EVENT REPORTING

Investigators should follow FDA regulations for the reporting of serious adverse events for commercial drugs. The NSABP does **not** need to be notified of any reports submitted for adverse events that occurred during the time the patient was taking letrozole provided through the Registration Program.

## 6.0 LETROZOLE DRUG INFORMATION

Please refer to the drug package insert and B-42 Protocol Section 9.0 for a description of letrozole and information on storage, toxicities, and precautions/warnings. Letrozole (Femara®) 2.5 mg tablets will be provided free of charge by Novartis Pharmaceuticals Corporation and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

### 6.1 Drug supply

Letrozole (Femara®; NSC #719345) will be supplied in bottles containing 30 – 2.5 mg tablets with child-resistant caps and tamper-evident seals. Each bottle represents a 1-month supply of drug, and each patient will receive an appropriate number of bottles to complete 5 years of initial adjuvant hormonal therapy (up to a maximum of 3 years of letrozole therapy or 36 bottles). This calculation is based on the amount of adjuvant hormonal therapy already completed by the patient at the time of enrollment in the Registration Program. Drug will be supplied in kits containing a 6-month supply of letrozole, and each kit will contain 6 bottles. Each bottle will be labeled with:

- the protocol number (i.e., 'NSABP B-42 Registration')
- the patient registration number
- the patient initials (e.g., 'LFM'; for NSABP B-42, this will be last initial, first initial, middle initial)
- the number of tablets (i.e., '30 tablets')
- bottle number (i.e., 1 of 36, 2 of 36, etc.). *Because a maximum of 3 years of letrozole may be supplied for a patient through the Registration Program, bottles will be labeled based on a total bottle count of "36". However, the total duration of letrozole supplied through the B-42 Registration Program will vary for each patient.*
- bottle start date
- bottle end date
- agent identification (i.e., 'letrozole [Femara®] 2.5 mg')
- administration instructions (i.e., 'Take one tablet once daily')
- storage instructions (i.e., 'Store at controlled room temperature [15°C to 30°C, 59°F to 86°F]')
- emergency contact instructions
- a Julian date.

In addition, the bottle labels will have a line for the individual dispensing the medication to enter the patient's name.

The Julian date indicates the day the bottle was shipped and is composed of the last two digits of the calendar year (e.g., 2006 = 06, 2007 = 07) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle shipped on January 1, 2006, would have a Julian date of 06001, and a bottle shipped on December 31, 2007, would have a Julian date of 07365. The Julian date will be used for recalls. When a lot expires, the PMB will determine the last date on which that lot was shipped and will recall everything shipped on or before that date.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

- Drug orders for NSABP and CTSU Investigators:

  Note: This information applies to drug orders for patients enrolled in the Registration Program for the B-42 study. For letrozole/placebo drug orders for patients enrolled in the randomized B-42 study, see Section 9.0 of the B-42 protocol.

  ***No starter supplies will be available for the Registration Program.*** Once a patient has been registered with the NSABP Biostatistical Center, the NSABP Biostatistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the NSABP Biostatistical Center the day the patient is registered. It will be processed by the PMB the next business day and shipped the following business day. The initial shipment for each patient will be sent by US Priority Mail (generally 2-3 day delivery) for US sites and by FedEx (generally 1-2 days delivery) for Canadian sites. Thus, if a patient is registered on Monday, the NSABP would enter a clinical drug request for that patient on Monday and the PMB would process the request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order either Friday or Monday, and Canadian sites could expect to receive their order either Thursday or Friday.

  All bottles will be sent to the treating investigator (unless otherwise specified by the local institution). The responsible investigator at each participating institution must be registered with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF). Sites may ship drug directly to the patient if necessary, but not to another physician's office. If shipping drug to the patient, it is recommended that a mail service that tracks the package and provides a return receipt be used (e.g., certified mail, FedEx). The initial request will be for 6 bottles each containing 30 tablets of letrozole (i.e., a 6 month supply). In addition, approximately 5 months after the patient is enrolled (i.e., 1 month before needed), an additional 6 bottles will be automatically ordered by the NSABP. Every 6 months thereafter (always approximately 1 month before needed), the next set of 6 bottles will be automatically ordered by the NSABP and sent to the nucleus institution or satellite institution that entered the patient **unless a treatment form, indicating that the patient has discontinued letrozole, has been received by the NSABP Biostatistical Center**. Due to the NSABP's automated drug ordering system, study personnel will not be required to submit an NCI Clinical Drug Request Form to obtain letrozole through the Registration Program.

### 6.2 Drug transfers

Bottles **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 institution to another participating institution) 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 CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient registration number and the patient's initials (e.g., 'LFM') should be entered in the 'Received on NCI Protocol Number' and the 'Transferred to NCI Protocol Number' fields in addition to the protocol number (i.e., 'NSABP B-42'). The participating institution should also inform the NSABP Biostatistical Center of the transfer.

### 6.3 Drug returns

**Only undispensed drug supplies should be returned to the NCI Clinical Repository.** When it is necessary to return the letrozole provided through the Registration Program (e.g., sealed bottles remaining if a patient permanently discontinues her participation in the Registration Program or expired bottles recalled by the PMB), investigators should return the letrozole to the NCI Clinical Repository 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 registration number and the patient's initials (e.g., 'LFM') should be entered in the 'Lot Number' field. A separate line item is required for **each** patient ID. **Opened bottles with remaining tablets should be documented in the patient-specific investigational agent accountability record (i.e., logged in as "returned by patient" and logged out as "for destruction") and destroyed on-site in accordance with institutional policy.**

### 6.4 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 CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate investigational agent accountability record must be maintained for each patient registration number on this protocol.

## 7.0 PATIENT ENROLLMENT AND WITHDRAWAL PROCEDURES

### 7.1 Patient consent form

Before the patient is enrolled on the B-42 Registration Program, the consent form (see Appendix C), including any addenda, must be signed and dated by the patient and the person who explains the Registration Program to that patient.

## 7.2 Enrollment

### 7.2.1 *NSABP Investigators*

Note: NSABP investigators who also are registered with the CTSU must enroll B-42 Registration Program patients through the NSABP; they are not permitted to enroll patients through the CTSU.

**Patient enrollment instructions can be found in the "Patient Entry Guidelines" section of the Members' Area of the NSABP Web site,** https://members.nsabp.pitt.edu.

### 7.2.2 *CTSU Investigators*

CTSU investigators must follow procedures outlined in Appendix B, Section 1.0, *Site Registration and Patient Entry for CTSU Investigators.*

## 7.3 Patient registration number

After all of the eligibility criteria have been met, the institution will receive the patient's registration number assigned for the Registration Program. This number will identify the patient for the Registration Program only. A unique patient study number will be assigned at the time of randomization on the B-42 study, if the patient chooses to participate in that study.

## 7.4 Patient-initiated discontinuation of treatment

Even after a patient agrees to take part in the B-42 Registration Program, she may stop treatment at any time. If treatment is stopped, final data forms for the Registration Program should be submitted.

## 7.5 Withdrawal from the Registration Program

If a patient chooses to have no further interaction regarding the B-42 Registration Program, the investigator must provide the NSABP Biostatistical Center with written documentation of the patient's decision to fully withdraw from the Program.

## 7.6 Investigator-initiated discontinuation of letrozole

The investigator may require a patient to discontinue letrozole if one of the following occurs:

- the patient develops a serious side effect that she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet Registration Program requirements, or
- new information about letrozole or other treatments for breast cancer becomes available.

## 8.0 REQUIRED FORMS AND MATERIALS

Worksheets for the forms needed for online enrollment and discontinuation of drug shipment for the Registration Program are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu. (CTSU investigators should refer to Appendix B and the NSABP B-42 Web page located on the CTSU Registered Member site.)

## APPENDIX B

## CANCER TRIALS SUPPORT UNIT (CTSU) INSTRUCTIONS

These instructions supplement the protocol for CTSU participants. The protocol is to be followed in areas not described in this appendix.

### 1.0 SITE REGISTRATION AND PATIENT ENTRY FOR CTSU INVESTIGATORS

*Note 1: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment.*

*Note 2: As of January 6, 2010, the NSABP B-42 randomized treatment trial closed to patient accrual following achievement of the sample size goal. Data collection for the NSABP B-42 randomized treatment trial continues as planned.*

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site (http://members.ctsu.org) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 am and 4:30 pm Eastern Time. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the NSABP B-42 Web page on the CTSU Member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study is listed as 'approved' in the CTSU RSS.

*Requirements for NSABP B-42 site registration:*

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet

#### 1.1 Optional B-42 Registration Program

*Requirements for patient enrollment in the optional Registration Program for NSABP B-42:*

- Patient must meet all inclusion criteria and no exclusion criteria should apply (see Appendix A)
- Patient has signed and dated the consent for the Registration Program (see Appendix C)

*CTSU procedures for patient enrollment in the optional B-42 Registration Program:* Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voice mail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e., within one hour, call the Registrar cell phone at 1-301-704-2376. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Form REG (Registration Form) for the Registration Program with necessary attachments
- Properly signed and dated consent form for the B-42 Registration Program

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m. Monday-Friday, Eastern Time (excluding holidays). Registrations received after 5:00 p.m. will be processed the next business day. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will access the NSABP on-line registration system to obtain assignment of a unique patient registration number (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

1.2 **B-42 randomized study**

*Requirements for patient enrollment on the main NSABP B-42 randomized study:*

All site staff (Lead Group [NSABP] and CTSU sites) will use the Oncology Patient Enrollment Network (OPEN) to enroll patients on the B-42 study. OPEN can be accessed at https://open.ctsu.org/open or from the OPEN tab on the CTSU Registered Member Web site.

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 NSABP or CTSU Web site as a tool to verify eligibility.
- All patients have signed and dated an appropriate consent form (see Appendix D) and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff must 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 Registered Member Web site.
- To perform registrations, the site user must have been assigned the “Registrar” role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, 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.

- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU Registered Member Web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for the patient's research records. Additionally, a transmittal form to be used when faxing the signed consent form to the NSABP Biostatistical Center will be provided.

Further instructional information is provided on the CTSU Registered Member Web site via the OPEN tab or at https://open.ctsu.org/open. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

*04/16/14* 2.0 **DRUG ORDERS FOR CTSU INVESTIGATORS**

CTSU investigators should refer to Section 9.0 of the protocol for detailed instructions on drug procurement, formulation, storage, accountability, and administration for the randomized study and to Appendix A for the Registration Program.

Commercial letrozole and blinded letrozole and matching placebo will be provided free of charge by Novartis Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP).

**No commercial or blinded starter supplies will be available for this study.**

"Letrozole" (for the Registration Program) and "letrozole/placebo" (for the randomized study) will be automatically requested for each patient by the NRG Oncology SDMC and will be shipped directly to the investigator registering/randomizing the patient on the study. Both commercial letrozole and blinded letrozole/placebo should arrive within seven to ten days of registration/randomization (see Section 9.0 of the protocol). Please note that the PMB will ship drug only to the shipping address specified by the CTSU investigator on their Supplemental Investigator Data Form.

*05/30/07*
*04/16/14* 3.0 **SPECIAL MATERIALS**

3.1 **Submission of tissue by CTSU investigators**

Tumor blocks are required from the primary index tumor (or positive lymph node if primary tumor block is not available). CTSU investigators should follow protocol directions for tissue procurement and submission to the NRG Oncology SDMC. NSABP Form BLK must accompany the paraffin blocks.

3.2 **Submission of blood/serum by CTSU investigators**

No blood/serum collections are required.

*05/30/07*
*04/16/14*

## 4.0 DATA SUBMISSION FOR CTSU INVESTIGATORS

All case report forms (CRFs) associated with this study must be downloaded from the NSABP B-42 Web page located on the CTSU Registered members site (https://www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the NRG Oncology SDMC. Submission of study data directly to the NRG Oncology SDMC is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at webmaster@nsabp.pitt.edu for an account. When submission of supporting documentation to the NRG Oncology SDMC is required, fax to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

The NRG Oncology SDMC will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the NRG Oncology SDMC and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.

Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the NRG Oncology SDMC.

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## 5.0 ADVERSE EVENT (AE) REPORTING BY CTSU INVESTIGATORS

Note that there are **NO** requirements to submit AE reports to the NRG Oncology SDMC during the Registration Program (see Section 5.0 of Appendix A). Specific reporting requirements for NSABP B-42 are found in protocol Section 10.0. The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was required for reporting adverse events for protocol B-42 through December 31, 2010. Utilize CTCAE v4.0 beginning January 1, 2011. A link to the CTCAE is available on the CTSU Member Web site. CTSU investigators should employ definitions of adverse events as described in Section 10.0 of the protocol. All reporting must be conducted within the time frames specified in Section 10.0, and all completed forms should be submitted as outlined in Section 10.0.

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for the oversight of the patient.

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### 5.1 Routine reporting

- CTSU institutions: please refer to Section 10.7 of the protocol and the protocol-specific routine reporting of adverse events form (B-42 Adverse Event Form) for instructions regarding routine adverse event reporting during the B-42 randomized study. If indicated, supporting documentation must be included with Adverse Event Form submissions. The Adverse Event Form is to be completed by the CTSU institution and sent to the NRG Oncology SDMC.
- CTSU institutions: please refer to Sections 10.8 and 10.9 of the protocol for instructions regarding reporting selected adverse events and second primary malignancies on the B-42 Follow-up Form.

- There are no routine AE reporting requirements during the B-42 Letrozole Registration Program (see Appendix A).

*04/16/14* 5.2 **Expedited reporting**

- Refer to Section 10.3 and Table 3 for instructions regarding expedited adverse event reporting requirements.
- Contact the NRG Oncology B-42 Research Nurse Specialist at the NRG Oncology SDMC (refer to Information Resources, page 9) for questions regarding completion of reports, the need for supporting documentation, and submission time constraints.
- Follow the instructions in Section 10.0 of the protocol when CTEP-AERS reporting is required. Access the CTEP-AERS electronic Web-based application and complete it fully and accurately. CTEP-AERS reports are submitted electronically to the NRG Oncology Lead Group, and available supporting documentation is faxed to the NRG Oncology SDMC (412-622-2113) at the time of the CTEP-AERS submission. Include the patient's study number and the CTEP-AERS ticket number on all supporting documentation.
- During the Registration Program, investigators should follow FDA regulations for the reporting of adverse events for commercial drugs. The NRG Oncology SDMC does **not** need to be notified of any reports submitted during the Registration Program.

*12/07/10*
*04/16/14* 5.3 **Secondary leukemia and myelodysplastic syndrome reporting**

Refer to protocol Section 10.4 for instructions on reporting secondary leukemia and myelodysplastic syndrome via CTEP-AERS. The NRG Oncology Research Nurse Specialist will submit the CTEP-AERS report and supporting documentation to the NCI.

5.4 **Pregnancy occurring while the patient is on study drug**

*05/30/07*
*04/16/14*

If a patient becomes pregnant while receiving study drug notify the NRG Oncology Clinical Coordinating Department.

## 6.0 REGULATORY AND MONITORING

*04/16/14* 6.1 **Study audit**

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Registered Member Web site.

### 6.2 Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-US HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU Web site.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

### 6.3 Clinical Data Update System (CDUS) monitoring

This study will monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

## APPENDIX C

### Optional NSABP B-42 Registration Program Sample Consent Form

# OPTIONAL NSABP PROTOCOL B-42 REGISTRATION PROGRAM: Registration Program to Provide Up to Three Years of Letrozole to Postmenopausal Women with Hormone Receptor Positive Breast Cancer Who Have Received at Least Two Years of Initial Adjuvant Hormonal Therapy

*01/23/09*
*02/04/10* *Note 1: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment.*

*02/04/10* *Note 2: As of January 6, 2010, the NSABP B-42 randomized treatment trial closed to patient accrual following achievement of the sample size goal. Data collection for the NSABP B-42 randomized treatment trial continues as planned.*

**Important Note:** As described in Appendix A, patients may enroll in the Registration Program for NSABP B-42 to complete 5 years of initial adjuvant hormonal therapy. **However, patients are not required to participate in the Registration Program in order to enroll in the main B-42 randomized study**. The NSABP will notify sites when accrual to the Registration Program is closed. Instructions will be provided at that time for patients still participating in the Registration Program, but who will not be able to be enrolled into the randomized study because the accrual goal for B-42 had been achieved. ***The consent form in Appendix C must be used for patients enrolling in the optional B-42 Registration Program of the study. The consent form in Appendix D must be used for all patients enrolling in the B-42 randomized study.***

Consent (Optional Registration Program) Version: September 12, 2007
To be attached to Protocol Version: April 16, 2014

**Instructions to Local Institutional Review Boards Regarding Local IRB Review of Multicenter Clinical Trials**

In order to conform to OHRP guidelines (effective November 9, 1992) regarding local IRB review of multicenter clinical trials, and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial.

The protocol and sample consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the sample consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. **The investigator is responsible for forwarding copies of substantive IRB-approved changes with their justifications to the NSABP Operations Center Division of Regulatory Affairs immediately.** It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff and government agencies.

## NSABP SAMPLE CONSENT (Optional Registration Program)

**Registration Program to Provide Up to Three Years of Letrozole to Postmenopausal Women with Hormone Receptor Positive Breast Cancer Who Have Received at Least Two Years of Initial Adjuvant Hormonal Therapy**

***(Note: Centers outside of the U.S. and Canada must insert the applicable country and government oversight agencies in place of the FDA and Health Canada where appropriate throughout the consent form.)***

Your doctor will explain this Registration Program to you. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more information.

### Why have I been asked to take part in this Registration Program?

You are being asked to take part in this program because you are a postmenopausal woman who has had breast cancer with a positive estrogen and/or progesterone (ER/PgR) receptor test *and* because you have been receiving hormonal therapy for at least 2 years to help prevent the cancer from returning. Although you have no evidence of cancer now, it is still possible that the breast cancer may return. Research has shown that there is a better chance of breast cancer not returning if a woman receives 5 years of hormonal therapy (either tamoxifen or an aromatase inhibitor [AI]). This is called adjuvant hormonal therapy. It is also known that, for postmenopausal women, taking an AI after some tamoxifen, or instead of tamoxifen, is even more beneficial. In this program, we are providing postmenopausal women with the hormonal therapy drug letrozole, which is an AI.

If you join this program you will be provided the AI, letrozole, free of charge to complete 5 years of adjuvant hormonal therapy. Once you have finished a ***total*** of 5 years of adjuvant hormonal therapy (including what you have already received before you join this program), you will then be asked if you would like to participate in a research study being conducted by the NSABP called B-42. If you decide to participate in this Registration Program, you will not be required to participate in the B-42 study when you complete 5 years of adjuvant hormonal therapy. ***The decision to take part in the B-42 study will be entirely up to you at that time.***

### Who is offering this Registration Program?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is offering this program.

***(The NSABP institution or CTSU investigator must supply appropriate information as to who is conducting the program locally.)***

**Why is this Registration Program being done?**

The main purpose of this program is to increase the number of postmenopausal women who have received the hormonal therapy drug letrozole as part of their adjuvant hormonal therapy for breast cancer treatment. The NSABP is offering this program so that we can have a larger group of women participating in the main study, NSABP B-42, who have received letrozole as part of their initial adjuvant hormonal therapy. The women who complete their initial adjuvant hormonal therapy on this program will then be asked to take part in the B-42 research study. The main purpose of the B-42 research study is to learn if taking *5 additional years of letrozole* after completing 5 years of initial adjuvant hormonal therapy (which included an AI) will help prevent breast cancer from coming back.

**How many people will take part in the Registration Program?**

We do not know how many people will agree to take part in this program. The number could be several hundred to several thousand patients from different cancer treatment centers.

**What will happen if I take part in this Registration Program?**

*Before you begin the Registration Program*: You will not need to have any exams, tests, and procedures in order to join the program. However, your doctor may want to do some exams, tests, and procedures as part of regular cancer care. This will be up to your study doctor.

*During the Registration Program*: If you meet the conditions to enroll in the Registration Program and you choose to take part, you will then be provided letrozole through this program. You will take one letrozole tablet (2.5 mg) by mouth every day for up to 3 years. You will only take letrozole until you complete 5 years of initial adjuvant hormonal therapy (this 5 years includes the hormonal therapy you received before you joined this program).

During the program, there are no tests or procedures ***required***. However, your doctor may want you to have some tests and procedures as part of regular cancer care. This will be up to your doctor.

**How long will I be on the Registration Program?**

Depending on how long you were taking hormonal therapy before you joined the program, therapy with letrozole will last from 6 months to up to a total of 3 years from the date you start taking letrozole. After you complete 5 years of adjuvant hormonal therapy (including what you received before you enrolled in this program), you will be asked if you would like to participate in the B-42 study that will look at whether or not taking 5 additional years of letrozole helps to further reduce the chance of breast cancer returning.

**Can I stop being in the Registration Program?**

Yes, you can decide to stop taking the letrozole provided through this Registration Program at any time. Tell your doctor if you are thinking about stopping, or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping, so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and tests will be most helpful for you.

**Can anyone else stop me from being in the Registration Program?**

Your doctor may stop you from taking part in this program at any time if he or she believes it is in the best interest for your health, if you do not follow the program guidelines, or if the program is closed by the NSABP.

**What side effects or risks can I expect from being in the Registration Program?**

You may have side effects while taking letrozole. These side effects are similar to side effects you may have had while taking hormonal therapy before joining this program. Talk to your doctor about the differences in the side effects for letrozole and the hormonal therapy drug you have been receiving.

Most of the letrozole side effects are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Your doctor will carefully watch you for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen some of the side effects. Many side effects go away soon after you stop taking the letrozole. In some cases, side effects may be very serious, long-lasting, or may never go away. *There is also a risk of death.*

You should talk with your doctor about any side effects that you may have while taking part in this program.

**Risks and side effects related to therapy with letrozole include those which are:**

***Likely***

These side effects occur in **25% or more** of patients receiving letrozole:

- Weakness or decreased energy
- Hot flashes/flushes

These side effects occur in **10-24%** of patients receiving letrozole:

- Increased cholesterol levels
- Increased sweating
- Swelling in hands or feet
- Constipation
- Dizziness
- Headache
- Joint pain/stiffness

***Less likely***

These side effects occur in **3-9%** of patients receiving letrozole:

- Difficulty sleeping
- Depression
- Hair loss or thinning
- Diarrhea
- Nausea
- Loss of appetite
- Bone fracture
- Drowsiness
- Muscle aches
- Back pain
- Shortness of breath
- Vaginal bleeding
- Vaginal dryness
- Osteoporosis, or bone thinning, a disease that can affect postmenopausal women. Letrozole may increase your chance of developing osteoporosis. Letrozole also may slightly increase your risk for bone fractures caused by osteoporosis. Talk with your doctor or nurse about your risk of developing osteoporosis, about tests that can detect osteoporosis, and about ways to prevent osteoporosis and fractures.

***Rare but serious***

These side effects occur in **less than 3%** of patients receiving letrozole:

- Heart problems, including narrowing of the blood vessels in the heart, chest pain, and heart attack have occurred in women receiving letrozole. However, the percentage of women developing these problems while taking letrozole was similar to the percentage of women receiving tamoxifen, which is an alternative hormonal therapy for breast cancer. In another study, the percentage was the same with women taking letrozole as with women taking a placebo (a pill that contains no active drug). This means that letrozole may not be associated with increasing the risk for heart problems, or it may be associated with a very small increase in risk. One of the aims of this study is to learn more about this risk.
- Blood clot in a blood vessel

For more information about risks and side effects, ask your doctor.

**Are there benefits to taking part in this Registration Program?**

Taking part in this program may or may not make your health better. Taking 5 years of adjuvant hormonal therapy, including taking letrozole, after your surgery is a standard treatment for your type of breast cancer.

**What other choices do I have if I do not take part in this Registration Program?**

Letrozole is available without being in this program. Your other choices may include:

- Getting treatment or care (including letrozole) without being in this program
- Getting no treatment

Please talk with your doctor about your choices before you decide if you will take part in this program.

*09/12/07*

**Will my medical information be kept private?**

As part of this program, your doctor will send the NSABP information about your cancer. This information will not be used for research unless you join the research study that will be offered to you when you complete this program. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Organizations that may look at and/or copy your medical records for quality assurance and data analysis include:

- the National Surgical Adjuvant Breast and Bowel Project (NSABP);
- the All Ireland Cooperative Research Group (ICORG)
- Novartis Pharmaceuticals Corporation, (the company that provides letrozole for this program);
- your local Institutional Review Board (IRB), a group of people who review this program to protect your rights;
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials; and
- government agencies, including the NCI or its authorized representatives, the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), Health Canada, and the Irish Medicines Board. These agencies may review the details of the program to see that it is being done safely and correctly.

**What are the costs of taking part in this Registration Program?**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer. Check with your health plan or insurance company to find out what they will pay for.

Novartis Pharmaceuticals Corporation, through the National Cancer Institute (NCI), will provide you with letrozole at no cost to you while you are taking part in this Registration Program. Every effort will be made to ensure adequate supplies of letrozole free of charge for all patients participating in this program. There is a slight chance that you and/or your health plan may have to pay for the letrozole if letrozole cannot continue to be provided through this program. Your doctor will discuss this with you if this occurs.

You will not be paid for taking part in this Registration Program.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

**What happens if I am injured because I took part in this Registration Program?**

It is important that you tell your doctor, _____***(insert doctor's name)***, if you feel that you have been injured because of taking part in this program. You can tell the doctor in person or call him or her at _____***(insert doctor's phone number).***

You will get medical treatment if you are injured as a result of taking part in this program. You and/or your health plan will be charged for this treatment. The Registration Program will not pay for medical treatment.

**What are my rights if I take part in this Registration Program?**

Taking part in this program is your choice. You may choose either to take part or not to take part. If you decide to take part, you may leave the program at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular medical benefits. Leaving the program will not affect your medical care. You can still receive your medical care from our institution.

We will tell you about any new information or changes in the program that may affect your health or your willingness to continue to take part in the program. You may be asked to sign another consent form in response to new information.

In the case of injury resulting from this program, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about this Registration Program?**

You can talk to your doctor about any questions or concerns you have about this program. Contact your doctor _____***(insert doctor's name and phone number).***

For questions about your rights while taking part in this program, call the _____ ***(insert the institution's name)*** Institutional Review Board (IRB) (a group of people who review research to protect your rights) at _____ ***(insert IRB phone number).***

***(If your institution is using the NCI Central IRB, insert the following sentence***: **You may also call the Operations Office of the NCI Central Institutional Review Board [CIRB] at 1-888-657-3711 [from the continental U.S. only].)**

**Where can I get more information about cancer and its treatment?**

- You may call the National Cancer Institute's (NCI's) Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615
- You may also visit the NCI Web site at http://cancer.gov
- For the NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For the NCI's general information about cancer, go to: http://cancer.gov/cancerinfo
- You may also visit the NSABP Web site at http://www.nsabp.pitt.edu

You will receive a copy of this form. If you want more information about this program, ask your doctor.

***(NSABP institutions or CTSU investigators may insert or attach a list of materials that they can provide locally to patients regarding clinical trials, drug information, the institution/investigator, and/or the NSABP or CTSU.)***

**Signatures**

I have been given a copy of all seven pages of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this Registration Program.

| | |
|---|---|
| _____ | _____ |
| Date | Patient's signature |
| _____ | _____ |
| Date | Signature of person conducting the informed consent discussion |

## APPENDIX D

### NSABP B-42 Sample Consent Form

# NSABP PROTOCOL B-42: A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer

*01/23/09*
*02/04/10* *Note 1: As of September 5, 2008, the optional NSABP B-42 Registration Program closed to patient enrollment.*

*02/04/10* *Note 2: As of January 6, 2010, the NSABP B-42 randomized treatment trial closed to patient accrual following achievement of the sample size goal. Data collection for the NSABP B-42 randomized treatment trial continues as planned.*

**Important Note:** As described in Appendix A, patients may enroll in the Registration Program of this study to complete 5 years of initial adjuvant hormonal therapy. **However, patients are not required to participate in the Registration Program in order to enroll in the main B-42 randomized study**. The NSABP will notify sites when accrual to the Registration Program is closed. Instructions will be provided at that time for patients still participating in the Registration Program, but who will not be able to be enrolled into the main study because the accrual goal for the B-42 study has been achieved. ***The consent form in Appendix C must be used for patients enrolling in the optional Registration Program of the study. The consent form in Appendix D must be used for all patients enrolling in the B-42 randomized study.***

Study Consent (randomized study) Version: September 12, 2007
To be attached to Protocol Version: April 16, 2014

**Instructions to Local Institutional Review Boards Regarding**
**Local IRB Review of Multicenter Clinical Trials**

In order to conform to OHRP guidelines (effective November 9, 1992) regarding local IRB review of multicenter clinical trials, and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial.

The protocol and sample consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the sample consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. Also, the NSABP Operations Center requires that, similarly, the NSABP also be notified of substantive changes in the consent form section regarding consent to collect and store samples for possible future testing. Of primary concern are text changes that could potentially affect the future usage of the banked samples. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. **The investigator is responsible for forwarding copies of substantive IRB-approved changes with their justifications to the NSABP Operations Center Division of Regulatory Affairs immediately.** It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff and government agencies.

## NSABP SAMPLE CONSENT (Randomized Study)

**A Clinical Trial to Determine the Efficacy of Five Years of Letrozole Compared to Placebo in Patients Completing Five Years of Hormonal Therapy Consisting of an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI in Prolonging Disease-Free Survival in Postmenopausal Women with Hormone Receptor Positive Breast Cancer**

***(Note: Centers outside of the U.S. and Canada must insert the applicable country and government oversight agencies in place of the FDA and Health Canada where appropriate throughout the consent form.)***

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more information.

### Why have I been asked to take part in this research study?

You are being asked to take part in this study because you had breast cancer with a positive estrogen and/or progesterone (ER/PgR) hormone receptor test *and* because you received 5 years of hormonal therapy to help prevent the cancer from returning. Some of your hormonal therapy was with a drug called an aromatase inhibitor (AI). Although you have no evidence of cancer now, it is still possible that your breast cancer may return. Therefore, you are being asked to take part in this research study to learn if receiving additional treatment after completing standard therapy will further reduce the chances of breast cancer returning.

### Who is conducting the study?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is conducting this study.

***(The NSABP institution or CTSU investigator must supply appropriate information as to who is conducting the trial locally.)***

*09/12/07*

### Why is this research study being done?

This study will look at the effects (good and bad) that letrozole has on you.

- The main purpose of the study is to learn whether or not continuing hormonal therapy with an AI called letrozole for 5 additional years after already taking 5 years of hormonal therapy (which included an AI) can further reduce the chance of breast cancer returning. Letrozole is investigational (still being researched) for use in patients who have already received an AI as part of their 5 years of hormonal therapy. Letrozole is considered "investigational" because it has not yet received approval from the Food and Drug Administration (FDA) or Health Canada for use after 5 years of hormonal therapy which included an AI.

An AI works by interfering with a substance called aromatase that helps to make estrogen. Estrogen is known to promote the growth of hormone receptor-positive breast cancers such as yours. An AI almost completely blocks out estrogen in postmenopausal women. By blocking out the estrogen levels, growth of tumors is blocked and the chance of breast cancer returning is smaller. In this study, you will be given letrozole or a placebo (a pill that looks like letrozole but does not contain any active drug) after 5 years of hormonal therapy. It is important to look at whether or not taking additional letrozole after already taking an AI affects how well letrozole works to continue to reduce the chances of cancer coming back.

- Another reason for doing this study is to find out whether or not taking the drug letrozole after taking 5 years of hormonal therapy that included letrozole (or other AI) causes more thinning of your bones (osteoporosis) which can cause your bones to break more easily. We also want to find out if letrozole increases the chance of heart attack, stroke, and other problems with blood vessels called arteries.

**How many people will take part in the study?**

About 3,840 women will take part in this study.

**What will happen if I take part in this research study?**

*Before you begin the study*: You will need to have the following exams, tests, and procedures to find out if you can be in the study. These exams, tests, and procedures are part of regular cancer care and may be done even if you do not join this study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- medical history and physical exam
- mammogram
- testing for bone mineral density (This is a test to measure the strength of bones.)
- blood tests to measure your cholesterol levels. These blood tests will be done because some patients in studies with letrozole have developed higher than normal cholesterol levels. Because studies have not confirmed if this is related to letrozole and because increased cholesterol levels are a common problem for postmenopausal women, your doctor will check your cholesterol before you join the study. Your doctor may also check these levels while you are receiving study therapy.

*During the study*: If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be "randomized" into one of the two treatment groups. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either of the two groups.

After you have joined the study, you will begin your study drug.

*If you are in Group 1:* You will take a placebo tablet that looks like the letrozole tablet but does not contain any active drug. You will take 1 tablet by mouth every day for 5 years.

*If you are in Group 2:* You will take a letrozole tablet (2.5 mg each day). You will take 1 tablet by mouth every day for 5 years.

Neither you nor your study doctor will know whether you are taking letrozole or placebo.

Summary of treatment:

| Group 1 | Group 2 |
|---|---|
| *Placebo*<br>*One tablet daily for 5 years* | *Letrozole 2.5 mg*<br>*One tablet daily for 5 years* |

During the study you will need to have the following tests and procedures. They are considered part of regular cancer care.

*During your treatment with letrozole/placebo:*

- history and a physical exam by your doctor about every 12 months. Also, every 6 months between your yearly exam by your doctor, your study doctor or other study personnel will check with you to see how you are doing on the study medication. This may or may not require an office visit or physical exam. This will be up to your study doctor.
- mammogram about every 12 months.
- bone mineral density testing about every 2 years. Your doctor may recommend this test be done more often, depending on the results of your previous bone mineral density tests.
- blood tests to check your cholesterol levels. How often these blood tests will be done depends on your cholesterol test results before you started taking the study drug. It also depends on whether or not you have any medical or family history that might mean you are at increased risk for developing heart problems in the future. You should discuss this with your study doctor.

*Other tests*

Your doctor may schedule other blood tests, bone mineral density testing, and other tests or procedures which are not required for this study but which your doctor believes are a part of good medical care to monitor your health while you are on the study. Discuss this with your study doctor.

*Other drugs your doctor may prescribe:*

Your doctor may recommend treatment with bisphosphonates, drugs which strengthen bone, depending on the results of your bone mineral density test(s).

Your doctor may recommend drugs to lower your cholesterol levels if the results of your cholesterol tests show that these levels are higher than normal.

*After you complete the letrozole/placebo, for the rest of your life:*

- contact from your study doctor or nurse about every 12 months to collect information about your health. This contact may be by phone with study personnel or during an office visit with your doctor.
- mammogram about every 12 months

*Optional tissue collection*

We would also like to have tissue samples from the surgery you had when your cancer was first diagnosed. These samples will be sent to the NSABP only if you agree to the tissue collection described at the end of this consent form.

**How long will I be on the study?**

Therapy with letrozole or placebo will last a total of 5 years from the date you start taking the tablets. We would like to keep track of your health for the rest of your life.

**Can I stop being in the study?**

Yes, you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and tests will be most helpful for you.

You can choose to withdraw in one of two ways. In the first, you can stop your study treatment, but still allow the study doctor to report your health status to the NSABP. In the second, you can stop your study treatment and request that no new information be reported to the NSABP.

**Can anyone else stop me from being in the study?**

The study doctor may stop you from taking part in this study at any time if he or she believes it is in the best interest for your health, if you do not follow the study rules, or if the study is stopped by the NSABP.

**What side effects or risks can I expect from being in the study?**

You may have side effects while on this study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Everyone taking part in the study will be carefully watched for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen some of the side effects. Many side effects go away soon after you stop taking your study drugs. In some cases, side effects may be very serious, long-lasting, or may never go away. *There is also a risk of death.*

You should talk with your study doctor about any side effects that you may have while taking part in the study.

**Risks and side effects related to therapy with letrozole/placebo include those which are:**

***Likely***

These side effects occur in **25% or more** of patients receiving letrozole:

- Weakness or decreased energy
- Hot flashes/flushes

These side effects occur in **10-24%** of patients receiving letrozole:

- Increased cholesterol levels
- Increased sweating
- Swelling in hands or feet
- Constipation
- Dizziness
- Headache
- Joint pain/stiffness

***Less likely***

These side effects occur in **3-9%** of patients receiving letrozole:

- Difficulty sleeping
- Depression
- Hair loss or thinning
- Diarrhea
- Nausea
- Loss of appetite
- Bone fracture
- Drowsiness
- Muscle aches
- Back pain
- Shortness of breath
- Vaginal bleeding
- Vaginal dryness
- Osteoporosis, or bone thinning, a disease that can affect postmenopausal women. The study drug may increase your chance of developing osteoporosis. The study drug also may slightly increase your risk for bone fractures caused by osteoporosis. Talk with your doctor or nurse about your risk of developing osteoporosis, about tests that can detect osteoporosis, and about ways to prevent osteoporosis and fractures.

***Rare but serious***

These side effects occur in **less than 3%** of patients receiving letrozole:

- Heart problems, including narrowing of the blood vessels in the heart, chest pain, and heart attack have occurred in women receiving letrozole. However, the percentage of women developing these problems while taking letrozole was similar to the percentage of women receiving tamoxifen, which is an alternative hormonal therapy for breast cancer. In another study, the percentage was the same with women taking letrozole as with women taking a placebo (a pill that contains no active drug). This means that letrozole may not be associated with increasing the risk for heart problems, or it may be associated with a very small increase in risk. One of the aims of this study is to learn more about this risk.
- Blood clot in a blood vessel

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in this study?**

Taking part in this study may or may not make your health better.

**What other choices do I have if I do not take part in this study?**

You have received standard therapy for your breast cancer. Currently, there is no approved therapy for cancer-free patients after 5 years of adjuvant hormonal therapy that included an AI. In breast cancer, adjuvant therapy is treatment that is given after breast surgery to lower the chance of cancer coming back. Although letrozole is available in the United States and Canada, it is not approved for use in patients who have already received 5 years of adjuvant hormonal therapy which included an AI. The FDA and Health Canada consider the use of letrozole in this setting to be investigational.

You may choose to receive no further treatment after already receiving 5 years of standard therapy. Please talk with your doctor about your choices before you decide if you will take part in this study.

*09/12/07* **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, for quality assurance, and data analysis include:

- the National Surgical Adjuvant Breast and Bowel Project (NSABP);
- the All Ireland Cooperative Research Group (ICORG);
- Novartis Pharmaceuticals Corporation, (the company that provides letrozole/placebo for this study);
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights;
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials; and
- government agencies, including the NCI or its authorized representatives, the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), Health Canada, and the Irish Medicines Board. These agencies may review the research to see that it is being done safely and correctly.

**What are the costs of taking part in this study?**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer during this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

*09/12/07* *Tests, procedures, or drugs for which there is no charge in this study:*

Novartis Pharmaceuticals Corporation, through the National Cancer Institute (NCI) will provide you with letrozole/placebo at no cost to you for this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

**What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, _____***(insert doctor's name)***, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or her at _____***(insert doctor's phone number).***

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

The Data Monitoring Committee (DMC), an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. You may be asked to sign another consent form in response to new information.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ ***(insert doctor's name and phone number).***

For questions about your rights while taking part in this study, call the _____ ***(insert the institution's name)*** Institutional Review Board (IRB) (a group of people who review the research to protect your rights) at _____ ***(insert IRB phone number).***

***(If your institution is using the NCI Central IRB, insert the following sentence***: **You may also call the Operations Office of the NCI Central Institutional Review Board [CIRB] at 1-888-657-3711 [from the continental U.S. only].)**

## Additional Studies

*The following section of the informed consent form is about additional research studies that may be done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you answer "no" to taking part in these additional studies.*

### What about the use of my tissue for research?

*About using tissue for future research*: The NSABP would like some of the tissue from the breast surgery you had when your cancer was first diagnosed. If you agree, the tissue samples will be sent to the NSABP Tissue Bank where the tissue will be kept and may be used in future research to learn more about cancer and other diseases. The tissue samples will be given only to researchers approved by the NSABP. Any research study using your samples must also be approved by an IRB. The research that is done with your tissue samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your tissue samples will not affect your care.

*Things to think about*: The choice to let the NSABP keep the tissue samples for future research is up to you. No matter what you decide to do, it will not affect your care. If you decide now that your tissue samples can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want the NSABP to use your tissue samples, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the NSABP decides to destroy them.

In the future, people who do research with your tissue samples and people who do other types of health-related research may need to know more about your health. While the NSABP may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue samples are used for genetic research (about diseases that are passed on in families). Even if your tissue samples are used for this kind of research, the results will not be told to you and will not be put in your health records.

Your tissue samples will only be used for research and will not be sold. The research done with your samples may help to develop new products in the future, but you will not get paid.

*Benefits*: The possible benefits of research from your tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them. The research that may be done with your tissue is not specifically designed to help you, but it may help people who have cancer or other diseases in the future.

*Risks:* The greatest risk to you is the release of information from your health records. The NSABP will protect your records so that your name, address, phone number, or any other information that may easily identify you will be kept private. The chance that this information will be given to someone else is very small.

There will be no cost to you for any tissue collected and stored by the NSABP.

**Making your choices**

Please read each question below and think about your choice. After reading each question, circle "yes" or "no." If you have questions, please talk to your doctor or healthcare team member.

*Participation in the optional collection and use of tissue samples*: Remember, no matter what you decide about the ***optional*** collection and use of the tissue samples in this research study, you may still take part in the B-42 study.

1. My tissue samples may be kept by the NSABP for use in future research to learn about, prevent, or treat cancer.

   YES NO

2. My tissue samples may be kept by the NSABP for use in future research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   YES NO

*Contact in the future for other research:* Remember, no matter what you decide, you may still take part in the B-42 study.

3. My study doctor (or someone he or she chooses) may contact me in the future to ask me to take part in more research.

   YES NO

**Where can I get more information about cancer and its treatment?**

- You may call the National Cancer Institute's (NCI's) Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615
- You may also visit the NCI Web site at http://cancer.gov
- For the NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For the NCI's general information about cancer, go to: http://cancer.gov/cancerinfo
- You may also visit the NSABP Web site at http://www.nsabp.pitt.edu

You will receive a copy of this form. If you want more information about this study, ask your study doctor.

***(NSABP institutions or CTSU investigators may insert or attach a list of materials that they can provide locally to patients regarding clinical trials, drug information, the institution/investigator, and/or the NSABP or CTSU.)***

**Signatures**

I have been given a copy of all ten pages of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this research study.

| | |
|---|---|
| _____ | _____ |
| Date | Patient's signature |
| _____ | _____ |
| Date | Signature of person conducting the informed consent discussion |