Chapter 7:
Breast Cancer Treatment: NCI's Investment and Recent Progress

The goal of breast cancer treatment research is to dramatically improve management and outcome of all stages of the disease. *Charting the Course: Priorities for Breast Cancer Research*

Research leading to improved cancer treatment plays a prominent role in NCI's cancer portfolio. Treatment research aims to identify and exploit the most promising areas of science and technology to yield important new information that will lead to better therapeutic interventions. It spans activities ranging from discovery of new interventions in the laboratory, to preclinical testing of safety and efficacy in animal models, to phased clinical trials in cancer patients.

In its 1998 report, the Breast Cancer PRG identified several goals for treatment research that, if met, would dramatically improve the management and outcome of all stages of breast disease. These goals included increasing disease-free and overall survival, improving patient outcomes, lowering the incidence of secondary breast cancers, and improving access to the highest-quality medical care for all Americans. The PRG recognized that achieving these endpoints would require improvement in several areas and outlined five priorities in breast cancer treatment research that could guide this effort. For both localized and advanced breast cancer, the PRG stressed the importance of:

- Developing innovative biological approaches for the treatment of breast cancer
- Developing the expertise required for modern clinical investigation
- Facilitating the design and conduct of large-scale clinical trials
- Learning more about breast cancer biology to better predict the clinical course of disease and response to therapy
- Increasing public access to information regarding treatment options and clinical trials

The NCI has been responsive to these PRG priorities. In the years since the release of the PRG report, the NCI has supported a wide range of research projects, training programs, and clinical trials that address these treatment-related priorities. As a result, there has been an increase in the number of effective therapeutic drugs in clinical practice, the number of ongoing breast cancer clinical trials testing new agents, and the rate of patient accrual to these clinical trials. One of the most notable advancements over the past 5 years in breast cancer treatment has been the shift in focus from using high-dose systemic chemotherapy regimens to the development of targeted therapies that are more effective and less toxic. The field of targeted therapeutics was pioneered by the monoclonal antibody-based drug, trastuzumab (Herceptin®), which was approved in 1998 for treatment of Her2-overexpressing metastatic breast cancer. In the ensuing years, several other classes of novel anticancer drugs and targeted delivery systems, including aromatase inhibitors and immunoliposomal vehicles, have been developed and are currently undergoing preclinical and clinical testing. In 1999, the aromatase inhibitor exemestane (Aromasin®) was approved for the treatment of breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy, making it the fourth aromatase inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer.

Since the release of the 1998 PRG report, NCI has sponsored a major report that is relevant to recommendations of the Breast Cancer PRG for treatment. The report, *National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000*,[1] summarizes currently available data on the use of adjuvant therapy for breast cancer. A 14-member panel developed conclusions based on evidence presented by experts in medical oncology, radiation oncology, biostatistics, epidemiology, surgical oncology, and clinical trials. The panel concluded that women should only receive adjuvant hormonal therapy if their tumors express hormone-receptor protein. Most women with localized breast cancer should receive adjuvant polychemotherapy, regardless of lymph node, menopausal, or hormone-receptor status, because it

1 Published in the Journal of the National Cancer Institute. 2001 Jul 4;93(13):979-89.

improves survival. The panel also pointed to the critical need for trials to evaluate the role of adjuvant chemotherapy in women older than 70 years and the impact of its side effects on quality of life.

NCI's Investment and Response

From FY1998 to 2003, the NCI's extramural investment in research on breast cancer treatment has increased from $52.0 million to $108.2 million (Figure 7-1). This increase in funding corresponds to increases in the number of projects that are responsive to PRG priorities in treatment research.

Table 7-1 summarizes the NCI's responsiveness to the five Breast Cancer PRG research priorities for treatment. In addition, NCI's responsiveness to one of the original PRG priorities on breast cancer genetics is summarized in Table 7-1.[2]

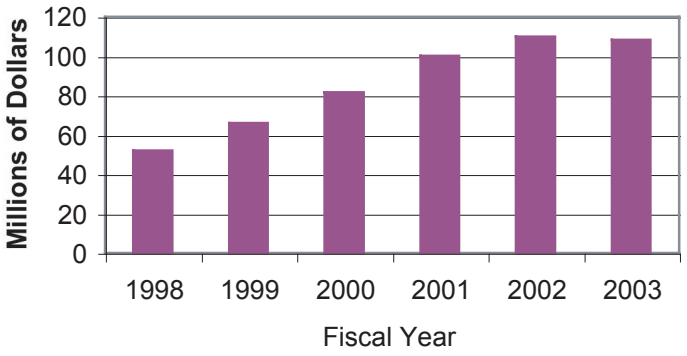
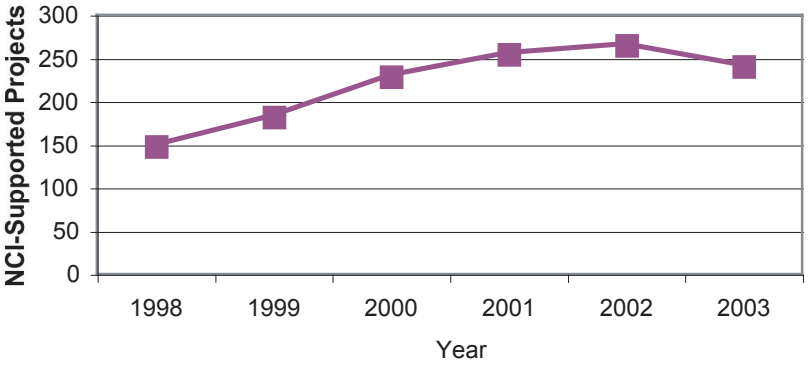


Figure 7-1. NCI's extramural investment in breast cancer treatment research: 1998-2003 (in millions of dollars)

Table 7-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Treatment

PRG Priority:

How can we develop innovative biological approaches to the treatment of breast cancer, in the laboratory and via small (pilot) trials?



NCI Efforts:

- In FY2003, examples of active areas of investigation included the association of a novel gene (*wth3*) with multidrug resistance; specific immunotherapy with monoclonal antibodies; novel cytotoxic products derived from marine sponges; biosynthesis of maytansinoids and analogs; drug discovery by mirror image ligand display; combinatorial creation of new anticancer agents; synthesis of WS9885B, a novel cytotoxic tubulin binder; novel therapeutic uses of phenylacetate in breast cancer; stress-induced bystander effects in cancer treatment; and preclinical evaluation of a novel apoptosis-inducing antitumor agent (MX2060).
- Examples of clinical trials addressing this priority included the following:
  - Phase I Pilot Study of Her2/*neu* Intracellular Domain Protein-Pulsed Autologous Dendritic Cells in Patients With Her2/*neu* Expressing Advanced Malignancies Showing No Evidence of Disease After Standard Treatment (DUMC-1309-00-7R1
  - Phase I Study of LMB-9 Immunotoxin in Patients With Advanced Colon, Breast, Non-Small Cell Lung, Bladder, Pancreas, or Ovarian Cancer (MSGCC-9981)
  - Phase I/II Randomized Study of Monoclonal Antibody CAL Versus Zoledronate in Women With Breast Cancer and Bone Metastases (CWRU-080235)

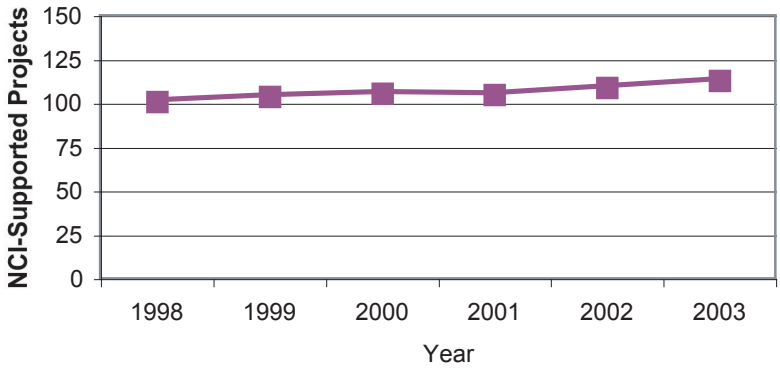
2 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-33 to B-39) by Principal Investigator's name for each PRG priority.

- Pilot Phase II study of sequential PANVAC-VF followed by the addition of docetaxel in metastatic breast cancer (LOI 6977 approved)
- Pilot Study to Evaluate Angiogenesis After Treatment With Bevacizumab (Anti-VEGF Humanized Monoclonal Antibody) in Previously Untreated Patients With Inflammatory Breast Cancer or Locally Advanced Breast Cancer (01-C-0173)
- Phase II Randomized Study of Anastrozole and Gefitinib Versus Fulvestrant and Gefitinib in Postmenopausal Women With Recurrent or Metastatic Hormone Receptor-Positive Breast Cancer (ECOG-4101)
- Phase Ib/II Neoadjuvant Study of Tipifarnib, Docetaxel, and Capecitabine in Patients With Locally Advanced or Metastatic Solid Tumors or Stage IIIA or IIIB Breast Cancer (NCI-5599)

- On September 28-29, 1999, NCI sponsored the first biannual *National Cancer Institute-Cancer Therapy Evaluation Program (CTEP) Drug Development Meeting*. On January 31-February 1, 2001, NCI Sponsored the *Workshop on Potential Clinical Applications for GnRH Antagonists*. On October 5–6, 2000, NCI sponsored a meeting on *Novel Molecular Targets for Cancer Therapy*.
- NCI initiatives addressing this priority included the Specialized Program of Research Excellence (SPORE) in Breast Cancer, Cancer Drug Discovery: Diversity Generation and Smart Assays, Cancer Therapy-Related Use of Genetically Engineered Mice, Clinical Proteomics Program (CPP), Exploratory Grants for Correlative Laboratory Studies and Clinical Trials, Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR), Molecular Target Drug Discovery for Cancer, National Cooperative Drug Discovery Groups (NCDDGs), Quick Trials for Novel Cancer Therapies, Rapid Access to Intervention Development (RAID) Program, Rapid Access to NCI Discovery Resources (RAND), Therapeutic Modulation of Angiogenesis in Disease, and Unconventional Innovations Program (UIP).

PRG Priority:

How can we facilitate the design and conduct of large clinical trials in breast cancer, focusing on the endpoints of longer disease-free and overall survival, reduced treatment toxicity, reduced breast cancer incidence, and ease of delivery to the entire population (including rural patients, the elderly, the economically disadvantaged, and members of minority groups)?



NCI Efforts:

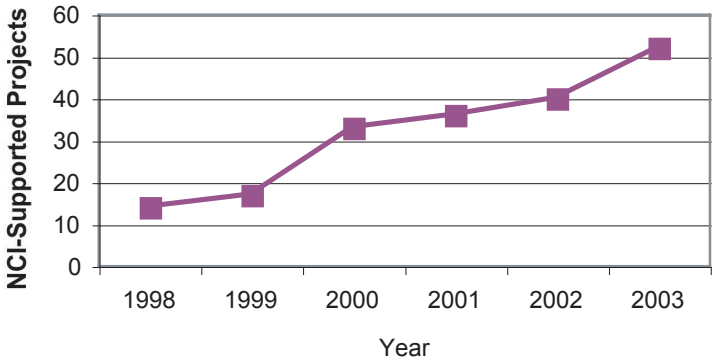
- In FY2003, examples of active areas of investigation included enhancing Native American participation in radiotherapy trials, understanding barriers to enrolling the elderly in cancer trials, evaluating cancer disparities among Hispanic communities, adjuvant hormonal therapy for Vietnamese women with breast cancer, simultaneous thermo-radiotherapy for breast carcinoma, and numerous trials conducted at clinical oncology program centers.
- Examples of clinical trials addressing this priority included the following:
  - Correlation of Menstrual Cycle Phase at the Time of Surgery With Disease-Free Survival in Premenopausal Women With Stage I or II Breast Cancer (NCCTG-N9431)
  - Phase III Randomized Study of Paclitaxel via One-Hour Infusion Every Week Versus 3-Hour Infusion Every 3 Weeks With or Without Trastuzumab (Herceptin®) in Women With Inoperable, Recurrent, or Metastatic Breast Cancer With or Without Overexpression of Her2/*neu* (CLB-9840)

- Phase III Prognostic Study of Sentinel Node and Bone Marrow Micrometastases in Women With Stage I or IIA Breast Cancer (ACOSOG-Z0010)
- Phase III Randomized Study of Neoadjuvant Docetaxel and Carboplatin With Versus Without Trastuzumab (Herceptin®) in Women With Locally Advanced Breast Cancer (UCLA-9911084)
- Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer (SWOG-S0221)
- Phase III Randomized Study of Letrozole Versus Placebo in Postmenopausal Women With Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen (MA.17)
- Phase III Randomized Study of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 and 21 Day Intervals in Women With Node-Positive Stage II or IIIA Breast Cancer (CALGB-9741).

- NCI initiatives addressing this priority included the Cancer Trials Support Unit (CTSU), Clinical Trials Cooperative Group Program, Community Clinical Oncology Program (CCOP), Cooperative Planning Grant for Cancer Disparities Research Partnership, Expanded Participation Project (EPP), and Minority-Based Community Clinical Oncology Program (MBCCOP).

PRG Priority:

How can we develop the expertise required for modern clinical investigation?

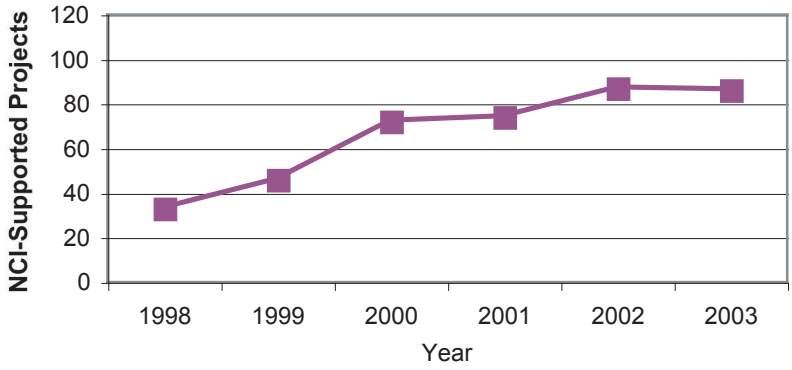


NCI Efforts:

- In FY2003, examples of active areas of investigation included a physician-scientist training program for clinical investigation protocol development, role of Her4 as a differentiation factor in breast cancer, clinical research in stem cell transplantation, education and training of surgical oncologists in the biologic basis of cancer and translational research, continued funding for a quality assurance review center, training physician-scientists to develop specific targets for therapy based on genetic and epigenetic alterations in cancer cells, semi-parametric and empirical process methods in oncology, urban Latino and African-American cancer disparities project, and a workshop on the nuclear radiology of breast cancer.
- On November 1-3, 2000, NCI sponsored the *Adjuvant Therapy for Breast Cancer-National Institutes of Health (NIH) Consensus Development Conference*. On April 26-28, 2000, NCI sponsored the *NIH Selective Estrogen Receptor Modulators (SERMs) Workshop*. On October 5-6, 2000, NCI sponsored *Novel Molecular Targets for Cancer Therapy*.
- The Center for Cancer Research at NCI provides training programs for postdoctoral fellows that focus on translational research projects in clinical oncology, cultural sensitivity training, and scientific management training.
- The recently introduced cancer Biomedical Informatics Grid (caBIG) is addressing some of these issues by assembling basic and clinical informatics tools that can be used widely by the cancer research community. In addition, caBIG is supporting the development of new tools by biomedical researchers.
- NCI initiatives addressing this priority included Breast SPOREs; Cancer Research Training, Career Development and Education Opportunities; Shared Resources for Scientists Outside NCI Cancer Centers; Special Populations Networks (SPNs); and Translational Research Initiative (TRI).

PRG Priority:

How can we learn more about the biology of breast cancer for the purpose of predicting clinical course and predicting response to therapy?

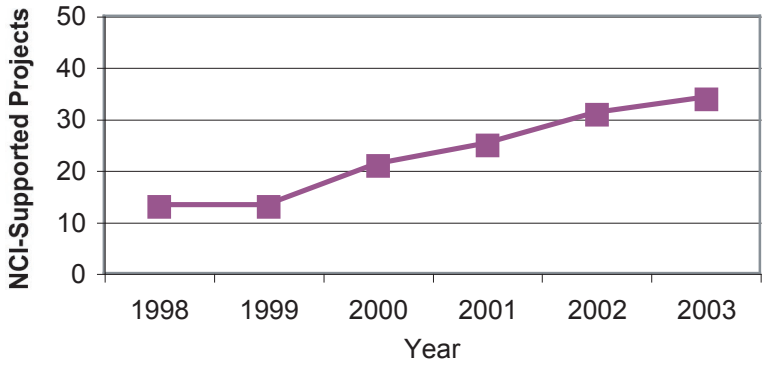


NCI Efforts:

- In FY2003, examples of active areas of investigation included evaluation of biologic endpoints and pharmacokinetics in patients with metastatic breast cancer after treatment with erlotinib, protein kinase C as a marker in tamoxifen-resistant breast cancer, defective estrogen receptors in breast tumors, the role of proteinase-3 in apoptosis and drug resistance, identification of paclitaxel-resistance genes, understanding how glutathione-s-transferase (GST) synergizes with the MRP toxin efflux transporter in multidrug resistance, and genetic modulation of cellular radiation responses.
- On December 4-5, 2003, NCI sponsored the *Linking Haplotypes and Genetic Variation With Cancer Risk Assessment, Prevention, Detection, and Treatment Workshop*.
- Clinical trials and related programs addressing this priority include:
  - Phase II Pilot Study of cDNA Microarray as a Measure of Tumor Response to Neoadjuvant Docetaxel and Capecitabine Followed by Surgery and Adjuvant Doxorubicin and Cyclophosphamide in Patients With Stage II or III Breast Cancer (NCI-00-C-0149)
  - Program for the Assessment of Clinical Cancer Tests (PACCT)
- NCI initiatives addressing this priority included the Cancer Molecular Analysis Project (CMAP), Cancer Prognosis and Prediction, and the Cooperative Human Tissue Network (CHTN).

PRG Priority:

Access to accurate information on treatment options, including available clinical trials, is critical for patients, their families, and providers.



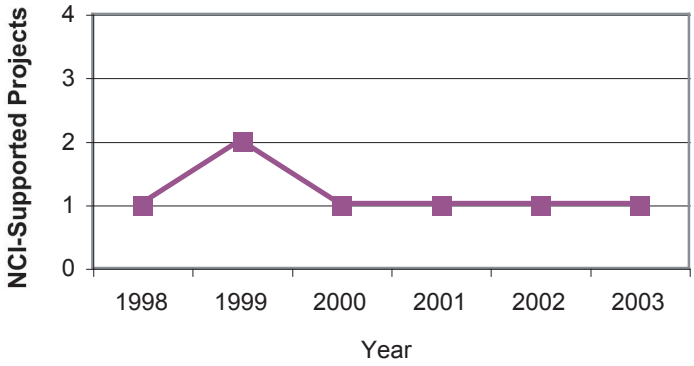
NCI Efforts:

- In FY2003, examples of active areas of investigation included the Urban Latino African-American Cancer Disparities Project, education and collaboration to enhance breast cancer care, the Partnership to Increase Hispanic Cancer Research Education, breast cancer patients' treatment preferences, enhancing Native American participation in radiotherapy trials, training minority scientists in research, overcoming barriers to early-phase clinical trials, educational and outreach approaches for cancer prevention, and improving cancer outcomes for African Americans.
- On August 27-29, 2003, NCI cosponsored the Trans-HHS Cancer Health Disparities Progress Review Group Roundtable.
- NCI resources that provide information about various types of cancer treatment options, including available clinical trials, include the Cancer Information Service (CIS), the NCI Publications Locator, and caMATCH, a computerized system for matching breast cancer patients with trials.

- NCI initiatives addressing this priority included the cancer Biomedical Informatics Grid (caBIG), Community Clinical Oncology Program (CCOP), Expanded Participation Project (EPP), Minority-Based Community Clinical Oncology Program (MBCCOP), Special Populations Networks (SPNs), and the Cancer Trials Support Unit.

PRG Priority:

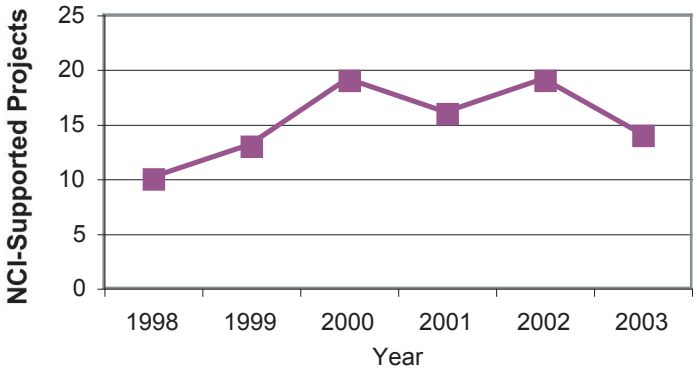
Are different recommendations for extent of surgery or reconstruction appropriate for women with an inherited predisposition?[a]



NCI Efforts:

- In FY2003, an active area of investigation was the national prospective study of risk-reducing salpingo-oophorectomy and ovarian screening among women at increased genetic risk of breast and ovarian cancer.
- NCI-funded researchers participate in the Prevention and Observation of Surgical End Points (PROSE) study group, an international clinical outcomes collaboration addressing the effectiveness of surgery on women with inherited predisposition to breast cancer.
- NCI initiatives addressing this priority included the Cancer Genetics Network (CGN) and Cancer Genetics Services Directory.

Additional Breast Cancer Treatment Projects



NCI Efforts:

- In FY2003, examples of active areas of investigation included percutaneous removal and margin ablation for breast cancer; induction of cell cycle arrest by clotrimazole—an inhibitor of RNA translation initiation; the role of the acetyltransferase *p300* in cellular responses; *p21* transcriptional inhibitors as proapoptotic compounds; healing touch, immunity, and fatigue in breast cancer; *grp78* and hypersensitivity to DNA cross-linking agents; and interleukin-10 for breast cancer therapy.
- Clinical trials and related programs addressing this priority include:
  - Phase II Randomized Study of Metronomic Low-Dose Cyclophosphamide and Methotrexate With or Without Bevacizumab in Women With Metastatic Breast Cancer (DFCI-03083).
- Research in the emerging area of image-guided therapies included magnetic resonance (MR) methods for guiding thermal therapy, anatomic and biologic staging of breast disease with MRI, integrated ultrasonic systems for noninvasive therapy, and MR-guided surgery and radiation therapy.

a. This priority was part of the Genetics section in the original Breast Cancer PRG report.

Clinical trials comprised a large part of the NCI's responsiveness to PRG priorities related to breast cancer treatment. A search of the Physician's Data Query Clinical Trials database for NCI-sponsored breast cancer treatment protocols identified nearly 300 clinical trials that were active between 1998 and 2003.[3] More than 130 of these trials were Phase I or Phase II investigations of innovative biological approaches for breast cancer treatment, and another 55 were large-scale clinical trials.

The initiatives that impacted breast cancer treatment research between 1998 and 2003 include the following list of general initiatives that are described in Table 2-1,[4] as well as the category-specific initiatives described in Table 7-2.[5]

- Aging Women and Breast Cancer
- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Basic and Preclinical Research on Complementary Alternative Medicine
- Bioengineering Research Grants
- Bioengineering Research Partnerships
- Breast and Ovarian Cancer Family Registries
- Breast Cancer Faculty
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Prognosis and Prediction
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Community Clinical Oncology Program (CCOP)
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Correlative Studies Using Specimens From Multi-Institutional Treatment Trials
- Developmental/Pilot Projects in Cancer Complementary and Alternative Medicine
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- Interdisciplinary Research Teams for Molecular Target Assessment
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs)

3 An NCI-sponsored clinical trial in the Physician Data Query (PDQ) database meets one or more of the following criteria: the protocol (1) has been reviewed and approved by NCI's CTEP Protocol Review Committee or by an approved NCI-designated Cancer Center Protocol Review and Monitoring System; and/or (2) receives support through an NCI grant or cooperative agreement. Information on ongoing treatment trials for the different stages of breast cancer can be obtained via the NCI's Clinical Trials Web page. To limit a search to only those trials that are sponsored by the NCI, it is necessary to use the advanced search function.

4 Initiatives that impact multiple categories of breast cancer research.

5 Initiatives that are unique to the treatment chapter.

- Minority Institution/Cancer Center Partnership (MI/CCP)
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Molecular Target Drug Discovery for Cancer
- NCI Center for Bioinformatics (NCICB)
- Nonmammalian Organisms as Models for Anticancer Drug Discovery
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small-Animal Imaging Resource Program (SAIRP)
- Small Grants Program in Cancer Epidemiology
- Special Populations Networks (SPNs)
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator
- Therapeutic Modulation of Angiogenesis in Disease
- Unconventional Innovations Program (UIP)

Table 7-2. NCI Initiatives Relevant to Breast Cancer Research: Treatment[a]

Initiatives With Breast Cancer-Relevant Components

- Cancer Drug Discovery: Diversity Generation and Smart Assays (RFA-CA-98-009)
  - Overview: Supports multidisciplinary teams of chemists and biologists who propose novel approaches to discover classes of compounds with potential anticancer activity.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, two projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Table B33, by searching for the current RFA number and the previously issued RFA number (RFA-97-006).
- Cancer Therapy-Related Use of Genetically Engineered Mice (PAR-02-051)
  - Overview: Supports the use of genetically engineered mouse models for cancer therapy-related goals.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this PA:

    Transgenic Mice as Models for Antivascular Therapy
- Cancer Trials Support Unit (CTSU) (http://www.ctsu.org)
  - Overview: Supports a national network of physicians to participate in NCI-sponsored Phase III clinical trials. Cooperative Clinical Trials Group sites within the United States and Canada are eligible for participation in the CTSU. In addition, the CTSU is now open to physicians and institutions in the United States that are not affiliated with a Cooperative Group.

a Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Relevant Clinical Protocols Resulting From This Initiative: Current CTSU-listed protocols for breast cancer include:

  Phase III Randomized Study of Axillary Lymph Node Dissection in Women With Stage I or IIA Breast Cancer Who Have a Positive Sentinel Node (ACOSOG-Z0011)

  Phase III Randomized Study of Adjuvant Cyclophosphamide and Doxorubicin Versus Paclitaxel in Women With Node-Negative Breast Cancer (CALGB-40101)

  Phase III Randomized Trial of Adjuvant Chemotherapy Comprising Standard Cyclophosphamide, Methotrexate, and Fluorouracil (CMF) or Doxorubicin and Cyclophosphamide (AC) Versus Oral Capecitabine in Elderly Women With Operable Adenocarcinoma of the Breast (CALGB-49907)

  Phase III Randomized Study of Paclitaxel With or Without Bevacizumab in Patients With Locally Recurrent or Metastatic Breast Cancer (ECOG-2100)

  Phase III Randomized Study of Ovarian Function Suppression in Combination With Tamoxifen Versus Ovarian Function Suppression in Combination With Exemestane Versus Tamoxifen Alone in Premenopausal Women With Endocrine-Responsive Breast Cancer (IBCSG-24-02)

  Phase III Randomized Study of Triptorelin and Exemestane Versus Triptorelin and Tamoxifen in Premenopausal Women With Endocrine-Responsive Breast Cancer (IBCSG-25-02)

  Phase III Randomized Study of Ovarian-Function Suppression and Tamoxifen or Exemestane With Versus Without Adjuvant Chemotherapy in Premenopausal Women With Endocrine-Responsive Resected Breast Cancer (IBCSG-26-02)

  Phase III Randomized Study of Adjuvant Breast Radiotherapy With or Without Regional Radiotherapy in Women With Previously Resected, Early-Stage Invasive Breast Cancer (CAN-NCIC-MA20)

  Phase III Randomized Study of Adjuvant Cyclophosphamide, Epirubicin, and Fluorouracil Versus Cyclophosphamide, Epirubicin, Filgrastim (G-CSF), and Epoetin Alfa Followed by Paclitaxel Versus Cyclophosphamide and Doxorubicin Followed by Paclitaxel in Premenopausal or Early Postmenopausal Women With Previously Resected Node-Positive or High-Risk Node-Negative Stage I-IIIB Breast Cancer (CAN-NCIC-MA21)

  Phase III Randomized Adjuvant Study of Exemestane Versus Anastrozole With or Without Celecoxib in Postmenopausal Women With Receptor-Positive Primary Breast Cancer (CAN-NCIC-MA27)

  Phase III Randomized Study of Adjuvant Doxorubicin and Cyclophosphamide Followed by Docetaxel Versus Doxorubicin and Docetaxel Versus Doxorubicin, Docetaxel, and Cyclophosphamide in Women With Breast Cancer and Positive Axillary Lymph Nodes (NSABP-B-30)

  Phase III Randomized Study of Adjuvant Clodronate With or Without Systemic Chemotherapy and/or Tamoxifen in Women With Early-Stage Breast Cancer (NSABP-B-34)

  Phase III Randomized Study of Anastrozole Versus Tamoxifen in Postmenopausal Women With Ductal Carcinoma *In Situ* of the Breast Undergoing Lumpectomy and Radiotherapy (NSABP-B-35)

  Phase III Randomized Study of Whole-Breast Radiotherapy Versus Observation With or Without Optional Tamoxifen in Women With Good-Risk Ductal Carcinoma *In Situ* of the Breast (RTOG-9804)

  Phase III Randomized Study of Standard Neoadjuvant Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Versus Weekly Doxorubicin and Daily Oral Cyclophosphamide With Filgrastim (G-CSF) Followed by Weekly Paclitaxel in Women With Inflammatory or Locally Advanced Breast Cancer (SWOG-S0012)

Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer (SWOG-S0221)

- Central Institutional Review Board (CIRB) (http://www.ncicirb.org/)
  - Overview: Supports an innovative approach to human subjects protection through a "facilitated review" process that can streamline local Institutional Review Board (IRB) reviews of national multicenter cancer treatment trials. A pilot project is currently sponsored by the NCI in consultation with the Department of Health and Human Services Office of Human Research Protections.
  - Relevant Results From This PA: Ten Cooperative Group-sponsored treatment protocols relevant to breast cancer have been approved by the CIRB since its inception in 2001.
- Clinical Cancer Therapy Research (PA-02-002)
  - Overview: Supports the translation of clinical cancer research insights and the development of new agents into innovative cancer therapeutic studies.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, four projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B6 and B33, by searching for the current PA number and the previously issued PA numbers (PA-99-046 and PA-92-069).
- Cooperative Planning Grant for Cancer Disparities Research Partnership (RFA-CA-03-018)
  - Overview: Supports the planning, development, and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low-income, ethnic, and minority populations but have not been traditionally involved in NCI-sponsored research.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, five projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Tables B34, B35, B37, B45, and B51, by searching for the current RFA number and the previously issued RFA number (RFA-CA-02-002).
- Development and Application of Imaging in Therapeutic Studies (RFA-CA-98-024)
  - Overview: Supports research projects that apply imaging technologies in the assessment of investigational cancer therapeutic agents.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, two projects relevant to breast cancer research were supported through this RFA.[b]
- Expanded Participation Project (EPP) (http://spitfire.emmes.com/study/epp)
  - Overview: Supports a demonstration project for providing broader access to Cooperative Group Phase III trials for breast and three other cancer types.
  - Relevant Programs Resulting From This Initiative: Twenty-eight participating institutions have centralized access to data from nine closed Phase III clinical trials on breast cancer.
- National Cooperative Drug Discovery Groups (NCDDGs) (http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html)
  - Overview: Supports broad, innovative, multidisciplinary approaches to the discovery of new synthetic or natural source-derived anticancer drugs.
  - Relevant Projects Resulting From This Initiative: Between 1998 and 2003, six projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Table B33, by searching for the RFA numbers RFA-CA-99-010, RFA-CA-95-020, and RFA-CA-94-007.

b Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Quick Trials for Novel Cancer Therapies (PAR-03-005)
  - Overview: Supports the rapid development of new therapeutic approaches and the assessment of these agents in pilot, Phase I, and Phase II cancer clinical trials through an accelerated review and funding process.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 11 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B24, B26, B33, B36, B39, and B51, by searching for the current PA number and the previously issued PA numbers (PA-00-047 and PA-99-070).
- Rapid Access to Intervention Development (RAID) Program (http://dtp.nci.nih.gov/docs/raid/raid_index.html)
  - Overview: Supports the translation of novel, scientifically meritorious therapeutic interventions from the academic community to the clinic.
  - Relevant Research Projects Resulting From This Initiative: Descriptions of RAID projects that have reached completion are available on the RAID Web site. To date, two breast cancer-relevant projects have been completed:

    A Study of Safety and Immunological Response of Immunotherapy in Patients With Solid Tumors

    Chemo-Immunotherapy for Metastatic Breast Cancer Treatment
- Rapid Access to NCI Discovery Resources (RAND) (http://dtp.nci.nih.gov/docs/rand/rand_index.html)
  - Overview: Supports academic and nonprofit investigators in the discovery of small molecules, biologics, or natural products with the potential for anticancer activity through such mechanisms as the development of high-throughput screening assays, computer modeling, recombinant target protein production and characterization, and chemical library generation.
  - Relevant Project Resulting From This Initiative: One project funded in the latest program cycle is using an MMTV-*neu* mouse model of breast cancer to screen for indoleamine 2,3-dioxygenase (IDO) inhibitors that mediate tumor regression.
- Translational Research Initiative (TRI) (http://ctep.cancer.gov/resources/trf-overview.html)
  - Overview: Supports correlative studies performed during the conduct of sponsored clinical trials of CTEP Investigational New Drug (IND) agents.
  - Relevant Programs Resulting From This Initiative: The TRI supports translational studies using samples from patients who participate in Phase I and Phase II clinical trials. Among the TRI-approved and/or supported protocols, the following are examples of clinical trials open exclusively to breast cancer patients:

    A Phase I Study of GTI-2040 and Capecitabine in the Treatment of Metastatic Breast Cancer

    A Phase Ib/II Neoadjuvant Trial of R115777 With Docetaxel and Capecitabine for Patients With Stage IIIA or IIIB Breast Cancer

    A Phase I-II Study of R115777 (Zarnestra) Plus Doxorubicin and Cyclophosphamide in Patients With Locally Advanced Breast Cancer and Metastatic Breast Cancer (P5598)

    A Phase I Study of Epothilone B Analog (BMS-247550) in Combination With Carboplatin in Recurrent and/or Refractory Solid Tumors

    A Phase II Trial of Primary Therapy With Bevacizumab and Docetaxel for Locally Advanced Breast Cancer

    Phase II Study of Neoadjuvant Doxorubicin, Docetaxel, and Bcl-2 Antisense (Genasense) Therapy for Patients With Locally Advanced Breast Cancer

    Phase II Trial of STI571 in Metastatic Breast Cancer

A Phase II Study of Depsipeptide in Patients With Metastatic Breast Cancer

A Phase II Study of Perifosine in Patients With Metastatic or Advanced Breast Cancer

Vaccination With Breast Cancer/Dendritic Cell Fusions in Conjunction With IL-12

Ongoing NCI Research: Progress in Breast Cancer Treatment

Progress in Preclinical Models

Recent advances in the development of transgenic mouse models displaying aspects of breast cancer disease progression have led to changes in the way promising therapeutic agents are tested. NCI-supported scientists have developed a transgenic mouse model of mammary cancer by expressing recombinant simian virus 40 early-region transforming sequences under the regulatory control of the rat prostatic steroid-binding protein [C3(1)] gene. This strain of mice, termed C3(1)/SV40 Tag, spontaneously develop tumors of the mammary epithelium without hormone supplementation or pregnancy (Maroulakou et al., 1994). Tumor progression in these mice follows a predictable time course and replicates several important stages that occur during human breast cancer progression, including noninvasive carcinoma, invasive carcinoma, and metastasis to bone. These mice provide good preclinical models for testing therapeutic compounds and have been used to demonstrate the effectiveness of several promising agents, including:

- Endostatin, which was shown to delay mammary tumor onset, inhibit the "angiogenic switch," and decrease tumor burden in these mice (Calvo et al., 2002).
- IL-12/pulse IL-2 treatment, which led to complete regression of established mammary carcinoma and prevented neovascularization in developing lesions (Wigginton et al., 2001), and 2-difluoromethylornithine (DFMO) and dehydroepiandrosterone (DHEA) combination, which was shown to inhibit mammary tumor progression in these mice (Green et al., 2001).

In Situ Disease

In situ breast disease—viewed as either noninvasive breast cancer or a precancerous condition—was an uncommon diagnosis until the widespread adoption of screening mammography. In 1998, about 18% of all new breast cancer diagnoses in the United States were identified as ductal carcinoma *in situ* (DCIS). Because a subset of DCIS patients goes on to develop breast cancer in the absence of treatment, the NCI has sponsored research on optimal treatment of *in situ* disease.

Although it was long thought that there was no role for postoperative therapy in the treatment of *in situ* disease, results from the B-24 trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP)—an NCI-funded clinical trials cooperative group—revealed that postsurgical tamoxifen is effective at preventing both invasive and noninvasive cancers in the ipsilateral (same) and contralateral (opposite) breasts of women with DCIS who have undergone breast conservation surgery followed by radiation (Fisher et al., 1999). In June 2000, the FDA approved tamoxifen (Nolvodex®)—an antiestrogen compound—as a postsurgical treatment for preventing invasive breast cancer in individuals with DCIS.

The NSABP B-35 trial is currently under way to determine whether postoperative anastrazole—a compound that prevents synthesis of estrogen by inhibiting the enzyme aromatase—is more effective than tamoxifen in preventing subsequent breast cancers in postmenopausal women with DCIS (Phase III Randomized Study of Anastrozole Versus Tamoxifen in Postmenopausal Women with Ductal Carcinoma *In Situ* of the Breast Undergoing Lumpectomy and Radiotherapy).

Operable Disease

Operable breast cancer, encompassing node-negative Stage I and Stage II disease and node-positive Stage II and Stage IIA disease, has traditionally been treated by a multimodal approach that includes surgery with or without subsequent radiation therapy for local control and, when deemed appropriate, postsurgical adjuvant hormonal and/or chemotherapy for systemic

control. NCI-sponsored researchers are attempting to refine all aspects of the traditional treatment paradigm: the specific treatments that are deemed appropriate, the order in which the treatments are administered, the duration and doses at which the treatments are administered, and the specific agents that are administered.

It has long been known that patients with operable node-positive disease are at higher risk for breast cancer recurrence than patients with node-negative disease and that node-negative patients with large tumors are at higher risk than those with small tumors. In the past, adjuvant therapy was not considered necessary for the majority of patients with node-negative breast cancers. The combined results of several NSABP trials have shown that node-negative tumors do benefit from adjuvant treatment (Fisher et al., 2001). In 235 estrogen receptor-negative patients, the 8-year relapse-free survival rate (RFS) was 90% in those who received surgery and adjuvant chemotherapy, compared with 81% in those who received surgery alone. In 1,024 estrogen receptor-positive patients, the 8-year RFS was 95% in those who received standard chemotherapy with tamoxifen, 93% in those who received tamoxifen alone, and 86% in those who received no adjuvant treatment. In another analysis of 1,009 women with tumors less than 1 centimeter in size, it was found that the combination of radiation and tamoxifen was more effective than either radiation or tamoxifen alone in reducing the ipsilateral recurrence rate following lumpectomy (Fisher et al., 2002).

Recently, new diagnostic tests, developed in part from NCI-supported tumor banks in the Cooperative Groups, are refining risk levels for patients with node-negative breast cancer. Women with node-negative breast cancer have an overall survival rate of approximately 70% following surgery alone. Adjuvant chemotherapy can improve the outcome for women destined to relapse. However, our inability to predict relapse has resulted in the overtreatment of a significant percentage of these women. NCI began the PACCT (Program for Assessment of Clinical Cancer Tests), which brought together experts from across the country to assist in the design of a trial to examine prognosis in node-negative tumors. As a result, the NCI-sponsored Cooperative Group, NSABP, in collaboration with an industrial partner (Genomic Health, Inc.), developed the Oncotype DXTM Breast Cancer Assay (Paik, 2003), which provides a recurrence score that correlates very well with 10-year disease-free survival. The PACCT Working Group endorsed the use of the Oncotype DXTM Assay in the trial they are proposing for women with node-negative tumors.

For patients with operable breast cancer, the order in which the various treatment modalities are administered has traditionally been definitive surgery followed by adjuvant chemotherapy (when applicable), followed by radiation (when applicable), and then tamoxifen (when applicable). In the past, preoperative or neoadjuvant therapy was reserved for patients with inoperable breast cancer to render their tumors operable. Recent NCI-sponsored research is defining the role of preoperative systemic therapies in patients with operable disease:

- Preoperative chemotherapy has demonstrated advantages over traditional postoperative adjuvant treatment and provides an opportunity for accelerated drug development. The NSABP B-18 trial demonstrated equivalent outcomes when chemotherapy is given before or after surgical resection of the primary breast tumor (Fisher et al., 1997). However, women with large tumors who had the chemotherapy first were able to undergo breast-conserving surgery more often than their counterparts. In addition, in this trial, the attainment of a pathologic complete remission (PCR) after four cycles of preoperative chemotherapy was strongly predictive of improved outcome. Thus, PCR may serve as a surrogate endpoint, thereby greatly accelerating the evaluation of new drugs and treatment approaches. This concept is being confirmed by the ongoing NSABP B-27 trial, which has completed enrollment and has demonstrated a higher PCR rate when docetaxel (Taxotere®) is given after the combination of doxorubicin (Adriamycin®) and cyclophosphamide (Bear et al., 2003). Disease-free and overall survival results from this trial are awaited to confirm that patients attaining PCR have the best outcome. In the interim, new trials are being designed by two Cooperative Groups to capitalize on this approach:
  - The NCI-supported American College of Surgeons Oncology Group is testing whether preoperative hormonal therapy can produce benefits for postmenopausal women with hormone-sensitive tumors, similar to that seen with preoperative chemotherapy.
  - The NSABP is evaluating new chemotherapy doublets following standard AC chemotherapy in a new preoperative clinical trial.

The trials described above will obtain tumor tissue before and after treatment to assess the genetic profile of the tumor and any changes that occur with therapy. This research should lead to genetic tumor profiles that can predict response to specific chemo-hormonal therapies.

NCI-sponsored clinical trials have continued to refine the doses, administration frequency, and duration of treatments used in patients with operable breast cancer.

- Improvements in radiation therapy may lead to increased utilization of breast-conserving surgery and an improved quality of life. Recent advances in radiation techniques have demonstrated that partial breast irradiation (PBI) given over 5 to 7 days may yield outcomes that are equivalent to the standard 6 weeks of external beam irradiation, which is typically given over the course of 30 visits to a radiation oncology facility (Baglan et al., 2003; Arthur et al., 2003). Two NCI-sponsored Cooperative Groups, NSABP and RTOG, are collaborating on a definitive trial in 3,000 women comparing standard whole-breast irradiation to PBI.
- The NCI-sponsored C9741 trial, performed by The Breast Cancer Intergroup of North America (TBCI), demonstrated that giving the same dose of chemotherapy drugs every 2 weeks instead of the standard every 3 weeks led to improved disease-free and overall survival of women with node-positive breast cancer (Citron et al., 2003). This novel study actually tested two concepts in one trial. The study used standard adjuvant chemotherapy drugs: doxorubin (A), cyclophosphamide (C), and paclitaxel (T). It compared the combination of AC followed by T (AC®T) to the sequential administration of A followed by T and then C (A®T®C) when given either every 2 weeks or every 3 weeks. There was no difference according to whether the drugs were given together or in sequence, but the every-2-week schedule improved both disease-free survival and overall survival at 36 months of median follow-up.
- The ongoing TBCI S0221 trial is determining whether there is benefit to using an even more "dose-dense" regimen. In this trial, the now standard every-2-week AC®T regimen is being compared to daily and weekly administration schedules (Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer).

Studies in patients with advanced breast cancer have shown prolonged survival following administration of hormonal therapies that specifically aim to interfere with estrogen stimulation or other tumor growth factors. Recent NCI-sponsored research has been directed at determining whether the therapies that prolong survival in patients with advanced disease are able to decrease the rate of disease recurrence in patients with early breast cancer.

- Aromatase inhibitors (AIs)—compounds that interfere with the synthesis of natural estrogen—were originally used as second-line hormonal therapy in postmenopausal women with estrogen receptor (ER)-positive metastatic breast cancer and later approved for first-line use, in lieu of tamoxifen, in the same patient group. Recent trials have shown that there is benefit to using AIs in adjuvant settings for women with ER-positive, early-stage disease. Ongoing and planned trials are addressing priorities regarding the optimal duration of AI treatment, whether AIs should replace tamoxifen or be used sequentially following completion of tamoxifen therapy, and whether one AI is superior to others with respect to efficacy and toxicity.
- The MA.17 trial, led by the National Cancer Institute of Canada, enrolled over 5,000 women, the majority of whom came from NCI-sponsored U.S. Cooperative Groups (Goss et al., 2003). The trial tested whether disease-free survival is extended by the addition of an AI, letrozole, after 5 years of adjuvant treatment with tamoxifen. Patients who were disease-free after 5 years of tamoxifen therapy were randomized to letrozole or placebo for 5 years. This study was stopped early because significant decrease in recurrence was observed compared with the placebo group. While letrozole seemed to result in a slight increase in osteoporosis, other side effects were generally mild and well tolerated. Further follow-up of long-term toxicity will be important.
- TBCI is leading the current MA.27 trial that directly compares two AIs, anastrozole and exemestane, to compare the event-free survival in postmenopausal women with receptor-positive breast cancer (Phase III Randomized Adjuvant Study of Exemestane Versus Anastrozole With or Without Celecoxib in Postmenopausal Women With Receptor-Positive Primary Breast Cancer).

- In September 1998, trastuzumab (Herceptin®) was approved by the FDA for treatment of metastatic breast cancer. After recognizing the effectiveness of Herceptin® in advanced breast cancer, NCI-supported Cooperative Groups moved quickly to launch two adjuvant trials—N9831 (Phase III Randomized Study of Doxorubicin Plus Cyclophosphamide Followed by Paclitaxel With or Without Trastuzumab [Herceptin] in Women With Her-2-Overexpressing Node-Positive or High-Risk Node-Negative Breast Cancer) and NSABP B-31 (Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel With or Without Trastuzumab [Herceptin] in Women With Node-Positive Breast Cancer That Overexpresses HER2)—to determine whether chemotherapy with Herceptin® is more effective than chemotherapy without Herceptin® in tumors that overexpress Her2/*neu*.
- Bisphosphonates are agents that interfere with bone osteoclasts and are able to disrupt the development of bone metastases from breast tumors. The bisphosphonate pamidronate (Aredia®) is approved in the U.S. for the treatment of advanced metastatic disease. NSABP is performing a definitive trial to test whether the oral bisphosphonate, clodronate, would prevent the development of bone metastases in the adjuvant setting (Phase III Randomized Study of Adjuvant Clodronate With or Without Systemic Chemotherapy and/or Tamoxifen in Women With Early Stage Breast Cancer). In addition, TBCI and NSABP are collaborating on a trial to compare clodronate, zoledronate, and ibandronate to determine whether there is a preferable bisphosphonate for the prevention of breast cancer metastases.

Nonoperable Disease

Nonoperable breast cancer, encompassing Stage IIIB and metastatic Stage IV disease, is treated systemically with first-line chemotherapy and/or hormonal agents. Second-line and subsequent treatments are attempted when first-line treatments are ineffective or when progression occurs in patients who had previously shown full or partial responses.

Although metastatic breast cancer is considered incurable, considerable effort has been directed at identifying treatments that prolong survival while maintaining quality of life. Patients with progressing metastatic breast cancer are generally the first population in which novel approaches and agents are tested for efficacy. Some of the new treatments examined in recent NCI-sponsored research include:

- The angiogenesis inhibitor, bevacizumab (Avastin®), in combination with paclitaxel as first-line treatment (Phase III Randomized Study of Paclitaxel With or Without Bevacizumab in Patients With Locally Recurrent or Metastatic Breast Cancer)
- The combination of fenretinide and tamoxifen (Phase III Randomized Study of Adjuvant Tamoxifen/Fenretinide Versus Tamoxifen/Placebo in Postmenopausal Women With Receptor-Positive Breast Cancer [Zujewski et al, 1999])
- The retinoid alitretinoin in combination with tamoxifen (Lawrence et al., 2001)
- The combination of all-trans retinoic acid and tamoxifen (Budd et al., 1998)
- The cell-cycle kinase inhibitor flavoperidol (Tan and Swain, 2002)
- R11557 (Zarnestra®), an inhibitor of protein farnesylation, in combination with the aromatase inhibitor letrozole (Zujewski et al, 2000)
- ZD1839 (Iressa®), an epidermal growth factor inhibitor, in combination with Herceptin® (Phase II Study of Trastuzumab (Herceptin®) and Gefitinib in Patients With Metastatic Breast Cancer That Overexpresses Her2-*neu*).
- Her2/*neu* vaccines (Disis et al., 2004)
- Anti-MUC-1 monoclonal antibody (Phase I Study of Vaccination Comprising Recombinant Vaccinia-MUC-1 and Recombinant Vaccinia-TRICOM Vaccine in Patients With Metastatic Breast Cancer)
- The apoptosis-inducing drug ceramide for treatment of cutaneous breast cancer (Phase II Study of Topical Ceramide Cream in Women With Cutaneous Breast Cancer).
- Topotecan for advanced breast cancer (Levine et al., 1999)

- Paclitaxel and carboplatin as first-line chemotherapy (Perez et al., 2000).
- The intracellular histamine antagonist N, N-diethyl-2-[4-(phenylmethyl) phenoxy] ethanamine (DPPE) and doxorubicin for patients with anthracycline-naïve metastatic breast cancer (Khoo et al., 1999).

Continuing Needs and Evolution

High priorities for breast cancer treatment research include the development of noninvasive approaches for primary breast cancer ablation and the development of targeted agents that are specific for the various molecular subtypes of breast cancer. Likewise, the discovery of nontoxic agents that block recently understood aspects of the estrogen receptor pathway is critical, as these agents can potentially be used with existing hormonal therapies to improve treatment response rates. Furthermore, efforts to understand patterns of drug sensitivity and resistance would be greatly facilitated by increasing the number of studies that systematically collect tissue samples before and after various therapies.

New areas for development in treatment-based imaging include image-guided applications to enhance intervention efficacy and integrating noninvasive imaging techniques to better appreciate the activity and mechanism of action of targeted therapies in Phase I and II studies. Additionally, newer clinical trial studies may include: (1) large, randomized studies that assign specific treatments based on new molecular parameters; (2) treatment studies in advanced disease based upon the early detection of micrometastases; and (3) smaller adjuvant trials that use pathologic complete response as a definitive endpoint (once this intermediate endpoint is established).

Progress in breast cancer treatment research would be enhanced by the establishment of standards of data collection that facilitate inter-Institute collaboration, data sharing, and leveraging of projects. The recently established cancer Biomedical Informatics Grid (caBIG) is a major development to facilitate these aims through standardization of computing tools, language, and resources for use by the cancer and biomedical research community. In a similar vein, enrollment in breast cancer treatment trials has been steadily improving over the past few years, ever since the establishment of the Cancer Trials Support Unit (CTSU). Breast cancer accounts for over 50% of all enrollments via this new NCI mechanism. The CTSU allows all qualified oncologists access to NCI-sponsored Phase III treatment trials, thereby speeding up the time to answer important questions and enhancing patient access to innovative therapies.

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