2008

Breast Cancer
Clinical Trials Resource Guide

A compendium of ongoing and proposed clinical trials evaluating biologic agents in the neoadjuvant, adjuvant and metastatic settings

Editor

Neil Love, MD

Clinical Trials

Neoadjuvant Therapy

- NSABP-B-40
- NSABP-B-41
- ACOSOG-Z1041
- Neo-ALTTO

Adjuvant Therapy

- NSABP-B-45
- BEATRICE
- US ONCOLOGY "TIC-TAC-TOE"
- ECOG-E5103
- ALTTO (BIG 2-06)
- NSABP/CIRG BETH

Metastatic Disease

- CALGB-40503
- CALGB-40302
- RIBBON 2 (AVF3693G)
- CAN-NCIC-MA31
- ECOG-E1105
- CLEOPATRA
- VEG108838
- SUN1064
- A6181094
- TRIO-012, CP12-0606

From the publishers of:
Breast Cancer® UPDATE

CME Certified

Breast Cancer Clinical Trials Resource Guide
A Continuing Medical Education Activity

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from clinical trials continuously lead to the emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care, the practicing medical oncologist must be well informed of ongoing and proposed clinical research opportunities, as these offer meaningful therapeutic options to many patients. This CME program is intended to inform and update medical oncologists on clinical trials of biologic agents in breast cancer and to encourage their enrollment of appropriately selected patients in these studies.

LEARNING OBJECTIVES

- Recall the design of ongoing and planned clinical trials evaluating biologic agents in the adjuvant, neoadjuvant and metastatic treatment of breast cancer.
- Explain the key scientific questions and molecular tumor subtypes that are currently being addressed through ongoing breast cancer research efforts.
- Appraise the standard and investigational treatment strategies that combine and/or sequence biologic agents with chemotherapy, endocrine therapy and other biologic agents.
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation.

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Table of Contents

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FACULTY — **Drs Burstein**, **Geyer** and **Wolmark** had no financial interests or affiliations to disclose. **Dr Gralow** — Consulting Agreements: Amgen Inc, Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, Sanofi-Aventis. **Dr Greco** — Advisory Committee: Bristol-Myers Squibb Company, Eli Lilly and Company; Paid Research: Eli Lilly and Company; Speakers Bureau: Eli Lilly and Company, GlaxoSmithKline. **Dr Mackey** — Honoraria: Amgen Inc, AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc, Sanofi-Aventis. **Dr Miller** — Consulting Agreements: Eli Lilly and Company, Genentech BioOncology, Roche Laboratories Inc; Paid Research: Pfizer Inc, Roche Laboratories Inc; Speakers Bureau: Genentech BioOncology, Roche Laboratories Inc. **Dr O'Shaughnessy** — Consulting Agreements: Biogen Idec, GlaxoSmithKline; Speakers Bureau: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Sanofi-Aventis. **Dr Perez** — Paid Research: Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation. **Dr Piccart-Gebhart** — Advisory Committee and Consulting Agreements: Bayer Pharmaceuticals Corporation, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr Sledge** — Consulting Fees: Genentech BioOncology; Contracted Research: Sanofi-Aventis. **Dr Swain** — Foundation Grant: Genentech BioOncology; Paid Research: Bristol-Myers Squibb Company; Paid Travel: Sanofi-Aventis.

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Faculty commentary included in this monograph was selected from previous *Breast Cancer Update* programs. To access our programs, please visit **www.ResearchToPractice.com**.

Editor's Note: Bail us out

"The NIH/CTSU studies — and this is not just my opinion — are not funded adequately to allow community oncologists to participate. It costs more to treat patients on clinical trials than is provided, so it's like docs are forced to subsidize the study. This is a major issue and one that is deeply frustrating."

— F Anthony Greco, MD
Lung Cancer Update

The enclosed reference piece highlights twenty ongoing studies attempting to move the field forward by evaluating the impact of a variety of targeted biologic agents in the management of early and advanced breast cancer. These trials test the clinical value of a number of new strategies and, like most current research efforts in oncology, include critical translational evaluations that will hopefully allow us to better understand the molecular basis for these interventions.

There is no shortage of ideas to pursue in this regard, but as noted by Dr Greco, there certainly is a dearth of resources that prevents these concepts from being executed. Tony's frustration as a US-based practitioner is easy to understand because clinical trial participation often puts investigators in the impossible position of wishing to be part of the solution but having to do so without adequate reimbursement for the services they provide.

The result was clearly evident during this year's ASCO plenary session, in which all four of the papers presented were research reports from Europe. The real travesty here is that somehow we found 700 billion dollars to bail us out of a financial mess that few of us actually understand, while we ignore a disease that each day strikes our patients without mercy.

The ideas being put forth in the studies profiled in this monograph represent a potential path to progress worthy of our focus and resources. It is time we increased our commitment to getting these studies done and new ones launched so that we can continue to dream up new ideas that will eliminate the personal catastrophes that are a daily part of oncology practice.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com

INVESTIGATOR COMMENTARY FOR SELECT TRIALS INCLUDED IN THE MONOGRAPH

NSABP-B-40

"NSABP-B-40 is a neoadjuvant study to follow up NSABPB-27, which added docetaxel in sequence to AC and resulted in the still intriguing and somewhat inexplicable doubling of the pCR rate but no advantage in terms of disease-free survival, recurrence-free survival, et cetera. NSABP-B-40 started out as a trial to assess the addition of capecitabine or gemcitabine to docetaxel, a straightforward three-arm trial. We decided to add a wrinkle by reversing the order and putting the taxane ahead of AC. We were close to activating NSABP-B-40 but decided that the bevacizumab data in metastatic disease were compelling and took it from a three-arm trial to a highly complicated study. It's now a three-by-two study of neoadjuvant therapy with a secondary randomization to bevacizumab or not."

— Charles E Geyer Jr, MD
Adjuvant Therapy for Breast Cancer:
Where We Are, Where We're Headed, 2008

"The novelty of NSABP-B-40 is that we're using pCR as an endpoint with an emphasis on developing a molecular taxonomy to determine whether we can characterize patients who obtain a pCR as a surrogate marker to measure outcome.

Disease-free and overall survival are not primary endpoints for NSABP-B-40. We view it as a new mechanism to test promising agents in the neoadjuvant setting, and we believe it is an appropriate direction to pursue, particularly with the number of agents that are available and the limited resources, both from a support standpoint and a population standpoint."

— Norman Wolmark, MD
Breast Cancer Update Issue 1, 2007

NSABP-B-45

"NSABP-B-45 will evaluate patients considered to be at high risk based on the observation that they did not achieve a pathologic complete response, either in the primary breast or in the axillary nodes, after preoperative therapy. Patients will be randomly assigned to one year of sunitinib or to placebo. This is an exciting setting in which to determine the value of a biologic agent for this patient population. Currently we do not have an algorithm to predict patient benefit in this particular subset, so robust tissue collection will be a prerequisite as we evaluate possible predictive markers for likelihood of benefit from sunitinib therapy."

— Norman Wolmark, MD
Breast Cancer Update Issue 5, 2008

BEATRICE

"We are launching the BEATRICE trial globally, which is for patients with triple-negative early breast cancer. This is a pragmatic trial that we designed together with a global team of investigators to explore the value of adding bevacizumab to chemotherapy in the adjuvant setting.

In the design of this trial basically any chemotherapy backbone is acceptable, because it's not addressing a chemotherapy question. It's a bevacizumab question. We believe, at least in the absence of administering concurrent trastuzumab, that you can safely administer bevacizumab with most of the chemotherapeutic cocktails we might use.

If the patient has a node-negative or a node-positive tumor and doesn't have distant metastases or rip-roaring cardiovascular disease or hypertension, then she will be randomly assigned on a one-to-one basis to bevacizumab or not. The one-year duration of the bevacizumab is purely arbitrary, and it begins with day one of chemotherapy.

We are hoping to see that anti-angiogenic therapy will make a difference in this population of patients with triple-negative disease. We do know that if you are to evaluate triple-negative tumors and compare them to all other comers, on average, one tends to see more VEGF production than in the nontriple-negative tumors. The other tumors that pop up with higher VEGF levels are the HER2-positive cancers."

— John Mackey, MD
Meet the Professors Breast Cancer,
Issue 1, 2008

"TIC-TAC-TOE"

"The rationale for combining bevacizumab with the nonanthracycline regimen TC in the "TIC-TAC-TOE" trial stems from the hypothesis that a HER2-negative population exists that does not need anthracyclines. Many groups are interested in that hypothesis, including US Oncology, Sarah Cannon, TORI and the NSABP. If indeed that is the case, then we want to see what bevacizumab contributes to a nonanthracycline regimen. This is similar to the BETH trial approach examining TCH and bevacizumab.

I want to add a cautionary note that I don't believe we are ready to drop anthracyclines without a prospective trial. We have decades of efficacy data with anthracyclines, so although I love the TC regimen, for patients with node-positive disease I believe that one of the proven three- or four-drug regimens — TAC, dose-dense AC/paclitaxel or FEC followed by docetaxel — is still the standard."

— Joyce O'Shaughnessy, MD
Breast Cancer Update Issue 5, 2008

"We have been in serious discussion with US Oncology about their "TIC-TAC" trial. NSABP will take the lead in adding onto that trial an arm called TOE. The trial will evaluate TC versus TAC versus TC and bevacizumab in women with node-positive or high-risk node-negative disease. I believe it's an important trial that will include bevacizumab without an anthracycline. Only one other study will have any data on that — the BEATRICE trial, which will evaluate seven adjuvant chemotherapy regimens with or without bevacizumab in patients with triple-negative disease."

— Sandra M Swain, MD
Adjuvant Therapy for Breast Cancer:
Where We Are, Where We're Headed, 2008

ECOG-E5103

"ECOG-E5103 is a large adjuvant study that encompasses several features. It has a practical element in that we allow patients and their physicians to select administration of AC every two weeks or every three weeks. We'll stratify for that choice, so it won't affect our results.

This design builds on the improvements we've made in adjuvant therapy in the past. The backbone of the chemotherapy is four cycles of AC followed by weekly paclitaxel. That's building on the ECOG-E1199 study, the adjuvant trastuzumab studies and the E2100 trial in the metastatic setting.

It's also incorporating preclinical data on the potential synergy between lower dose but more continuous taxane exposure and bevacizumab. In laboratory studies, at doses much lower than the doses that are required to have any direct cytotoxic effect on the tumor cells, the taxanes have a clearly separate effect on endothelial cells. To obtain that effect, however, you need more prolonged exposure. With weekly schedules, we have a lower dose but more continuous exposure to the drug."

— Kathy D Miller, MD
Breast Cancer Update Issue 5, 2008

ALTTO

"When we design these trials, we have a responsibility to ask interesting questions. With the ALTTO study, we felt that it was important to compare the relative merits of these anti-HER2 treatments.

The single-agent lapatinib arm has not made everyone comfortable, but we believe that the lapatinib data in metastatic breast cancer are encouraging. It is important to examine what a small molecule administered orally can do, as opposed to an antibody that must be administered in a hospital setting. In some countries in the world, it might be a problem to go to the hospital every three weeks for a full year.

The other arms are exciting. One of them is exploring the sequence of the two drugs — three months of trastuzumab, a short washout period and then lapatinib to complete a year of treatment. The third arm, which could be the winner, is the combination of the two agents.

We wanted this trial to reflect practices around the world. It's a major collaborative effort of more than 40 countries. Chemotherapy can be introduced in two ways. One is to administer the chemotherapy first, and you have a lot of flexibility in the choice of chemotherapy regimen.

The second option is the concurrent administration of the biologics with paclitaxel. We are probably going to introduce an option for concurrent docetaxel in the near future because we are beginning to have data there.

At present, the ALTTO trial is requiring patients to receive anthracyclines, but this may change also. We don't want to be in a situation when the trial is finished in which people tell us anthracyclines are no longer needed. We are strongly hoping to be able to allow regimens such as TCH to be used in the trial."

— Martine J Piccart-Gebhart, MD, PhD
Breast Cancer Update Issue 6, 2008

"ALTTO is a huge, international undertaking between the Breast International Group and the North American Breast Intergroup. The backbone chemotherapy can vary depending on where you live.

In the US, we will predominately use an anthracycline and then weekly paclitaxel, with four different ways of administering the HER2-targeted therapy: trastuzumab alone, lapatinib alone, both agents together or a sequence of the two agents with a washout period. Everyone receives one year of the HER2-targeted therapy. We will carefully examine the efficacy and toxicity with respect to the heart.

Much debate goes on about the single-agent lapatinib arm and whether it is ethical.

It's standard in this country to use trastuzumab in that setting: Are we omitting an effective therapy in favor of an as-yet unproven therapy? In the metastatic setting, the data with lapatinib are impressive. I've been increasingly reassured that there's activity, especially in combination with paclitaxel, as Angelo Di Leo presented at ASCO 2007."

— Julie R Gralow, MD
Breast Cancer Update Issue 3, 2008

BETH

"The BETH trial is a collaboration between the CIRG and NSABP examining a nonanthracycline-containing regimen combined with trastuzumab with or without bevacizumab. We feel strongly in the NSABP, as does Dr Slamon, about using nonanthracycline regimens. We chose TCH from BCIRG 006. The second interim analysis from that trial showed a significant benefit with TCH compared to AC-docetaxel. But, this is a large international collaboration with many investigators in Europe who don't belong to the CIRG or NSABP, and they wanted to include an anthracycline-containing regimen. So a cohort will receive docetaxel/trastuzumab-FEC with or without bevacizumab.

We hope the study will accrue quickly, because many physicians aren't comfortable with using anthracyclines anymore. I believe the data are convincing, especially if you consider BCIRG 006 and the Gennari meta-analysis showing that patients with HER2-negative disease don't benefit from anthracyclines and those with HER2-positive disease do. If you put all this together, you either need an anthracycline or trastuzumab for a patient with a HER2-positive tumor. Of course, we have chosen trastuzumab, not the anthracycline."

— Sandra M Swain, MD
Adjuvant Therapy for Breast Cancer: Where We Are, Where We're Headed, 2008

"The most exciting trial that we're conducting is the BETH trial, a collaborative effort between the NSABP and CIRG that is evaluating bevacizumab in combination with trastuzumab in the adjuvant setting for HER2-positive breast cancer. We proposed the idea because Dennis Slamon's laboratory found evidence of a profound synergistic interaction between those two drugs. In Phase I and then Phase II trials, they demonstrated tremendous efficacy with the two agents in advanced breast cancer. It was only logical to move it into the adjuvant setting. In the BETH trial design, we require that all tumors be submitted for central analysis prior to randomization to ensure true HER2 positivity. We will also examine a number of molecular markers, and we hope to tease out the subpopulation of patients who particularly benefit from the combination of trastuzumab and bevacizumab."

— John Mackey, MD
Breast Cancer Update Issue 1, 2008

RIBBON 2

"In relation to the issue of the timing of the introduction of bevacizumab for the treatment of metastatic breast cancer, we have the negative study of capecitabine with versus without bevacizumab in patients with previously treated metastatic disease and the positive ECOG-E2100 study of first-line paclitaxel with or without bevacizumab, which demonstrated improvements in response rate and progression-free survival. At this point, we don't have any solid data to justify routinely introducing bevacizumab in the second-line setting. However, RIBBON 2 is an important ongoing trial that plans to randomly assign 650 patients who have already received first-line chemotherapy to chemotherapy with or without bevacizumab."

— Edith A Perez, MD
Breast Cancer Update Issue 3, 2008

CLEOPATRA

"The CLEOPATRA trial is evaluating docetaxel with trastuzumab with or without pertuzumab in patients with previously untreated, HER2-positive metastatic breast cancer. Pertuzumab is an anti-HER monoclonal antibody, which prevents the dimerization of HER2 and HER3. We conducted a small study with pertuzumab and observed an 18 percent response rate in patients who were previously treated with trastuzumab. José Baselga's group also presented an update of their study, and the response rate was approximately 26 percent with the use of pertuzumab alone."

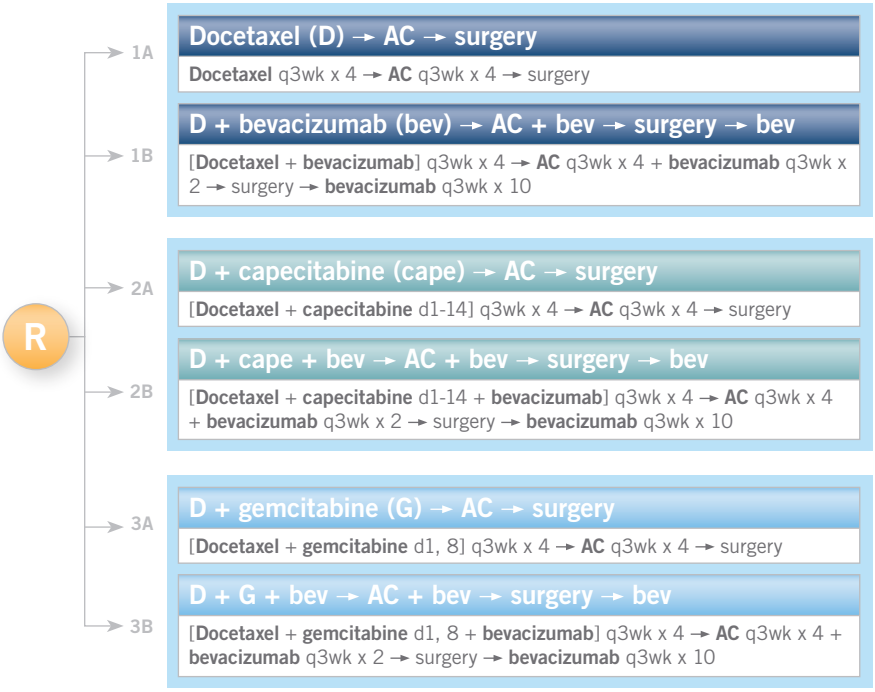
— Sandra M Swain, MD
Adjuvant Therapy for Breast Cancer: Where We Are, Where We're Headed, 2008

1 What is the optimal neoadjuvant therapy for patients with HER2-negative breast cancer?

NSABP-B-40

A Phase III randomized trial of six neoadjuvant regimens in patients with palpable and operable HER2-negative breast cancer

TRIAL DESIGN



Patients with ER/PR-positive disease receive a minimum of five years of hormonal therapy.

KEY FACTS

Select Eligibility Criteria
- Palpable breast mass ≥ 2.0 cm
- HER2-negative

Stratification
- Clinical tumor size (2.0-4.0 cm, >4.0 cm)
- Clinical nodal status (negative, positive)
- Hormone receptor status
- Age < 50, age ≥ 50

Primary Endpoint
- Pathologic complete response (pCR) rate in the breast

Secondary Endpoints
- pCR rate in axillary nodes, clinical complete and overall response rate, disease-free survival, toxicity, gene expression profile for predictors of response

Target Accrual: 1,200

Date Activated: November 2006

Estimated Completion Date: April 2012

Study Contact

NSABP
Harry D Bear, MD, PhD, Protocol Chair
Tel: 804-828-9325
Email: hdbear@vcu.edu
ClinicalTrials.gov Identifier: NCT00408408

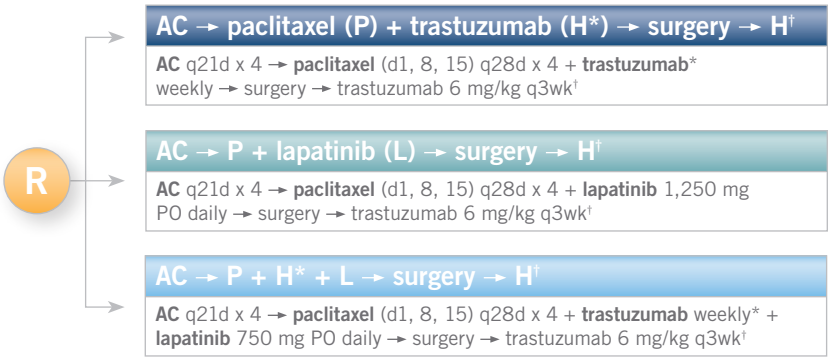
SOURCES: NSABP-B-40 Protocol, February 2008; NCI Physician Data Query, October 2008.

2 What is the optimal anti-HER2 agent/regimen combined with neoadjuvant chemotherapy for HER2-positive invasive breast cancer?

NSABP-B-41

A randomized Phase III trial of neoadjuvant therapy comparing trastuzumab, lapatinib and the combination administered with weekly paclitaxel after AC

TRIAL DESIGN



* IV weekly: 4 mg/kg loading dose, then 2 mg/kg weekly until 1-7 days before surgery

† Postoperative therapy (all patients): H 6 mg/kg IV q3wk until one year after first preoperative targeted therapy dose (H or L). If trastuzumab was not administered as part of neoadjuvant therapy, administer a loading dose of 8 mg/kg, then 6 mg/kg IV q3wk.

KEY FACTS

Select Eligibility Criteria

- HER2-positive invasive breast cancer
- ECOG PS 0 or 1
- Primary tumor ≥ 2.0 cm
- No prior therapy with anthracyclines, taxanes, trastuzumab or lapatinib for any malignancy
- No synchronous bilateral invasive breast cancer
- No metastatic disease

Stratification

- Tumor size (2.0-4.0 cm, >4.0 cm)
- Clinical nodal status (negative, positive)
- Hormone receptor status (ER-positive and/or PgR-positive, ER- and PgR-negative)
- Age < 50, age ≥ 50

Primary Endpoints

- Determine whether AC → P + H + L yields greater pCR rate than AC → P + H
- Determine whether AC → P + L yields greater pCR rate than AC → P + H

Secondary Endpoints

- Determine whether AC → P + H + L yields greater pCR rate than AC → P + L, compare corresponding pCR rates in the breast and nodes, clinical complete and overall response rate, recurrence-free survival, overall survival, cardiac and noncardiac toxicities of each regimen
- Tumor tissue studies: Comparison of array comparative genomic hybridization (CGH) data with gene expression profile data to examine coordinated overexpression of amplified genes, especially in HER2 and cMYC loci

Target Accrual: 522

Date Activated: July 2007

Estimated Completion Date: July 2014

Study Contacts

NSABP
Norman Wolmark, MD, Principal Investigator
Diana Gosik, RN, BS
Tel: 412-330-4692
Email: diana.gosik@nsabp.org

ClinicalTrials.gov Identifier: NCT00486668

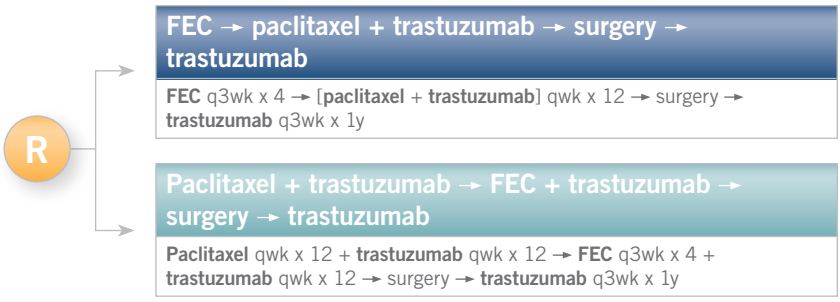
SOURCES: NSABP-B-41 Protocol, July 2008; **www.nsabp.pitt.edu**; NCI Physician Data Query, October 2008; **www.clinicaltrials.gov**.

3 What is the optimal sequencing of neoadjuvant therapy for patients with HER2-positive operable breast cancer?

ACOSOG-Z1041

A Phase III trial comparing a neoadjuvant regimen of FEC-75 followed by paclitaxel and trastuzumab to a neoadjuvant regimen of paclitaxel and trastuzumab followed by FEC-75 and trastuzumab in patients with HER2-positive operable breast cancer

TRIAL DESIGN



Other Therapy: Patients with ER-positive and/or PR-positive disease receive a minimum of five years of hormonal therapy.

KEY FACTS

Select Eligibility Criteria

- Invasive breast cancer with tumor size ≥ 2.0 cm
- HER2-positive by FISH or IHC (3+)
- ER and PR status known
- DCIS (synchronous contralateral, or previous ipsilateral or contralateral) allowed, except those treated with ipsilateral radiation therapy
- No metastatic disease
- No prior history of invasive breast cancer

Stratification

- Tumor size (2.0-4.0 cm, >4.0 cm)
- Age < 50, age ≥ 50
- Hormone receptor status (ER- and PR-negative, ER- and/or PR-positive)

Primary Endpoint

- pCR rate in the breast

Secondary Endpoints

- Cardiotoxicity, combined pCR rate in the breast and axillary lymph nodes, adverse events, disease-free survival and overall survival at five years postrandomization

Target Accrual: 391

Date Activated: July 2007

Study Contacts

American College of Surgeons Oncology Group
Aman Buzdar, MD, Protocol Chair
Tel: 800-392-1611
Kelly Hunt, MD, Protocol Co-chair
Tel: 800-392-1611
Email: khunt@mdanderson.org

ClinicalTrials.gov Identifier: NCT00513292

SOURCE: NCI Physician Data Query, October 2008.

"Numerous small phase II studies have shown that adding trastuzumab to preoperative chemotherapy achieves high pCR rates. The MD Anderson group conducted a small, randomized phase II preoperative trial of paclitaxel and FEC with or without trastuzumab in HER-2-overexpressing breast cancer. The pCR rate was 25% in the chemotherapy-only arm versus 67% in the chemotherapy-trastuzumab arm..." ■

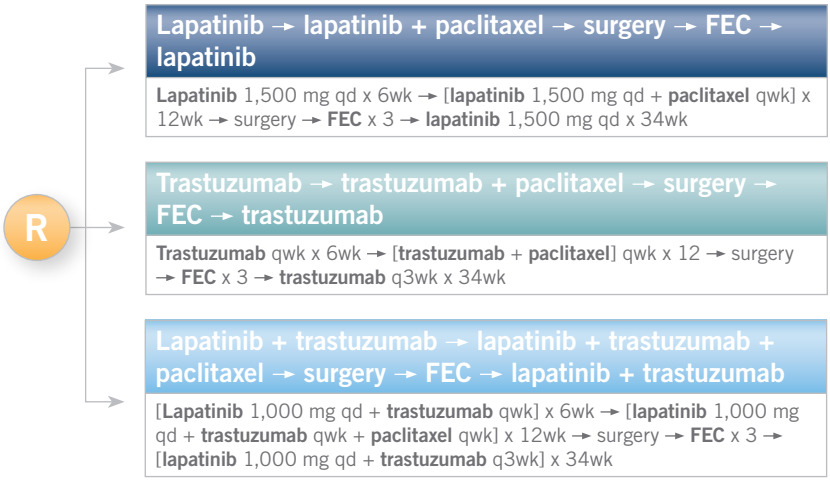
— Gralow J et al. *J Clin Oncol* 2008;26:814-9.

4 What is the optimal anti-HER2 neoadjuvant and adjuvant therapy for women with HER2-positive, nonmetastatic disease?

Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization) Study

A randomized, multicenter, open-label study of neoadjuvant lapatinib, trastuzumab and their combination with paclitaxel in women with HER2/ErbB2-positive primary breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Histologically confirmed invasive breast cancer
- Tumor > 2.0 cm
- Any N
- HER2 overexpression and/or amplification
- No evidence of metastasis (M0) (isolated supraclavicular node involvement allowed)
- Known hormone receptor status
- No prior treatment for invasive breast cancer
- No inflammatory breast cancer
- No bilateral cancer
- No previous neoplasms in past 10 years, except curatively treated basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix

Primary Endpoint

- Rate of pCR in breast at the time of surgery (18 weeks)

Secondary Endpoints

- Safety and tolerability
- Objective response rate
- Percent of patients with node-negative disease at surgery
- Conversion to breast conservation
- DFS and OS
- Biomarkers
- PET/CT

Target Accrual: 450

Date Activated: February 2007

Estimated Completion Date: September 2019

Study Contacts

Breast International Group
Email: ALTTOtrials@bordet.be
GlaxoSmithKline
Tel: 877-379-3718
Email: Lapatinibtrials.northamerica@gsk.com

ClinicalTrials.gov Identifier: NCT00553358

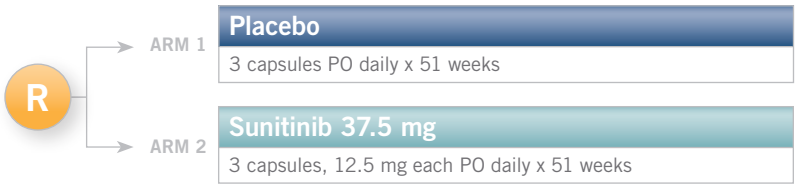
SOURCES: NCI Physician Data Query, October 2008; **www.breastinternationalgroup.org**.

5 Will sunitinib improve outcomes for women with residual invasive breast cancer after neoadjuvant chemotherapy?

NSABP-B-45

A Phase III clinical trial comparing adjuvant sunitinib malate to placebo after neoadjuvant chemotherapy*

TRIAL DESIGN



* Minimum of four cycles that included at least two of the following: an anthracycline, a taxane, cyclophosphamide

KEY FACTS

Select Eligibility Criteria

- Stage II, IIIA or IIIB (except T4d) invasive carcinoma before neoadjuvant therapy
- Residual invasive breast cancer after neoadjuvant therapy
- Neoadjuvant therapy with at least two of the following: an anthracycline, a taxane and cyclophosphamide
- HER2-negative disease

Stratification

- Hormone receptor status (ER-positive and/or PgR-positive, ER-negative and PgR-negative)
- Number of positive nodes (0, 1-3, 4+)
- Administration of postoperative chemotherapy (yes, no)
- Time from surgery to randomization (<3 months, 3-6 months)

Primary Endpoint

- Invasive disease- and DCIS-free survival improvement

Secondary Endpoints

- Survival, breast cancer-free interval, cardiac function, thyroid function, adverse events, quality of life, validation of residual risk determination methods, exploration of potential biomarkers of response

Target Accrual: 2,000 (pending activation)

Date Activated: Pending

Study Contact

NSABP
Tel: 412-330-4600

ClinicalTrials.gov Identifier: Not yet available

SOURCES: NSABP Protocol Summaries, June 2008; www.nsabp.pitt.edu.

"Clinicians and patients often wonder whether additional chemotherapy should be given in the adjuvant setting after preoperative chemotherapy treatment. To date, no trial has shown that additional chemotherapy after a modern preoperative chemotherapy (generally anthracycline- and taxane-based therapy) improves outcome...

Although there is no evidence that more chemotherapy will be of value, it is also fully recognized that this clinical situation [residual invasive breast cancer] is one that arises frequently in clinical practice, given that the majority of patients treated with preoperative therapy do not achieve a complete pathologic response. Outside of a clinical trial, the use of additional chemotherapy after a standard course of treatment should be discouraged. Within the context of a clinical trial, a variety of approaches could be tested in this setting, including the use of non–cross-resistant chemotherapy, angiogenesis inhibitors, high-dose bisphosphonates, vaccines, and a variety of other biologic therapies." ■

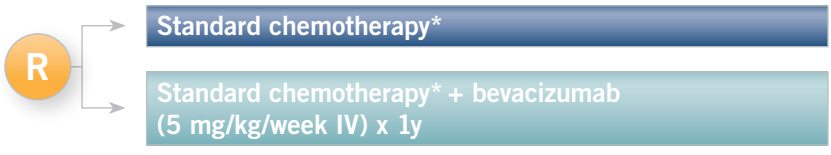
— Gralow JR et al. *J Clin Oncol* 2008;26:814-9.

6 Is the combination of bevacizumab with standard adjuvant therapy for triple-negative breast cancer safe and effective?

BEATRICE

A randomized, Phase III, open-label study of bevacizumab as adjuvant therapy for triple-negative disease

TRIAL DESIGN



* Anthracycline ± taxane or taxane only

KEY FACTS

Select Eligibility Criteria

- Adult patients (age ≥ 18 years)
- Operable primary invasive breast cancer
- Completed definitive locoregional surgery
- Primary tumor centrally confirmed as triple-negative
- No locally advanced breast cancer
- No previous breast cancer history
- No clinically significant cardiovascular disease

Primary Endpoint

- Invasive disease-free survival

Secondary Endpoints

- Overall survival
- Breast cancer-free interval
- Disease-free survival
- Distant disease-free survival
- Adverse events
- Laboratory parameters

Target Accrual: 2,530

Date Activated: December 2007

Estimated Completion Date: July 2014

Study Contact

Hoffman-LaRoche
Clinical Trials Study Director
Tel: 800-526-6367

ClinicalTrials.gov Identifier: NCT00528567

SOURCE: www.clinicaltrials.gov.

"There is basic and clinical evidence supporting the important role of angiogenesis in breast cancer. Although no specific overexpression of VEGF has been described in BLBC, there has been a morphologic description that such tumors have vascularity, potentially justifying VEGF as a suitable target in TNBC.

These findings are further supported by the results of a randomized phase III trial led by the Eastern Cooperative Oncology Group. E2100 compared paclitaxel with or without bevacizumab as front-line therapy in patients with metastatic breast cancer. Only 1% of patients were HER2-positive.

In a subset analysis, the addition of bevacizumab benefited several groups, including patients with ER-negative and PR-negative tumors. In this cohort, progression-free survival improved in the combination arm (8.8 months vs 4.6 months, hazard ratio 0.53).

With this encouraging clinical activity in the metastatic setting, bevacizumab is being tested in patients with early stage TNBC."

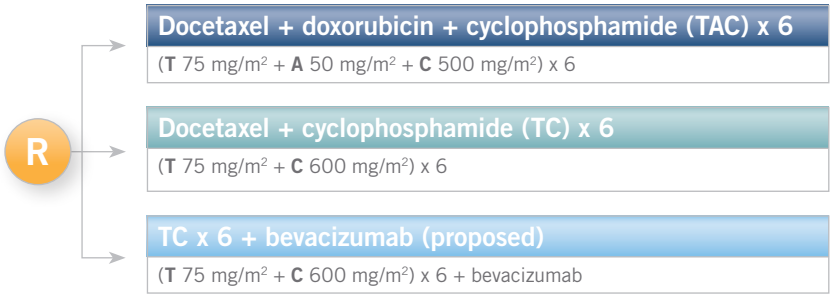
[BLBC = basal-like breast cancer; TNBC = triple-negative breast cancer]

— Wasserman EJ, Tan AR
ASCO Educational Book, 2008

7 Will bevacizumab add benefit to nonanthracycline adjuvant therapy? How does TAC compare to TC?

US Oncology "TIC-TAC-TOE"
NSABP proposed amendment to US Oncology 06090
A Phase III trial of adjuvant TC versus TAC versus TC/bevacizumab

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- HER2-negative breast cancer (FISH)
- Known ER and PR status
- Operable Stage I to IIIC breast cancer
- Meets one of the following criteria:
  - T1-3N1-3M0 if ER-positive or ER-negative
  - T2-3N0M0 if ER-positive or ER-negative
  - T1N0M0 if ER-negative and PR-negative
- No chemotherapy within five years
- Normal cardiac function

Primary Endpoint

- Three-year DFS

Target Accrual: 3,900

Date Activated: May 2007

Study Contacts

US Oncology Research
Joanne L Blum, MD, Principal Investigator
Tamara Orr
Tel: 832-348-5579
Laura Guerra
Tel: 832-348-5275

NSABP
Tel: 412-330-4600

ClinicalTrials.gov Identifier: NCT00493870

SOURCES: NCI Physician Data Query, October 2008; **www.clinicaltrials.gov**; Jones SE. *J Clin Oncol* 2007;25(27):4327. **Abstract**; Wolmark N. Personal communication. NSABP Group Meeting, June 2008.

"Sarah Cannon and US Oncology are evaluating six cycles of TAC versus six cycles of TC, but will that be a definitive trial? The target sample size is 2,000 patients, and the study has 80 percent power to detect a 3.4 percent absolute difference in disease-free survival in favor of the anthracycline. What if the difference is only three percent and the *p*-value is 0.08? What conclusions will we derive?

So the NSABP, along with Steve Jones and US Oncology, would like to fold that trial into the 'TIC-TAC-TOE' trial, or the 3T trial, in which we're comparing TAC to TC to TC/bevacizumab in 3,900 patients.

We hope the last arm will determine whether bevacizumab on a nonanthracycline template can add benefit, and it will increase the sample size for the pairwise comparison of TAC to TC to approximately 3,600, which would provide more power to determine the value of an anthracycline or the lack thereof in a HER2-negative cohort." ■

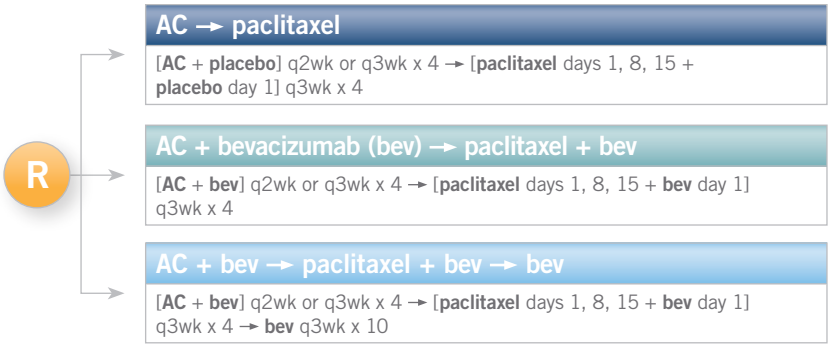
— Norman Wolmark, MD
Breast Cancer Update Issue 5, 2008

8 Does bevacizumab add benefit to chemotherapy for high-risk early breast cancer?

ECOG-E5103

A Phase III study of adjuvant AC followed by paclitaxel with or without bevacizumab

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- ER and PR status known, HER2-negative
- Node-positive or high-risk, node-negative
- Patients enrolled on ECOG-PACCT-1 (TAILORx) with ER-positive tumor ≥ 1 < 5 cm, RS ≥ 11 allowed

Primary Endpoint

- Disease-free survival (DFS)

Secondary Endpoints

- DFS
- Overall survival; toxicity

Target Accrual: 4,950

Date Activated: November 2007

Estimated Completion Date: November 2013

Study Contacts

Eastern Cooperative Oncology Group
Kathy D Miller, MD, Protocol Chair
Tel: 888-600-4822
Email: kathmill@iupui.edu
Ramona Swaby, MD, Protocol Co-chair
Tel: 888-369-2427

North Central Cancer Treatment Group
Donald Northfelt, MD, FACP, Protocol Chair
Tel: 507-538-7623
Email: cancerclinicaltrials@mayo.edu

Cancer and Leukemia Group B
Chau Dang, MD, Protocol Co-chair
Tel: 800-525-2225

ClinicalTrials.gov Identifier: NCT00433511

SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov.

"I believe that bevacizumab will be effective in the adjuvant setting, but hypotheses with evidence exist on both sides of the question. Angiogenesis may be regarded as one of the earliest events that a tumor cell must accomplish. We see evidence of angiogenesis even in DCIS, in which the tumors are not yet invasive. It is an early phenomenon, which suggest that agents like bevacizumab might be more effective earlier in the course of the disease, which would bring you into the adjuvant setting. I also have questions about the duration of therapy. We administer bevacizumab for two durations in E5103: approximately six months and approximately one year. Perhaps that's not long enough. Perhaps you need chronic therapy, not to eliminate microscopic disease but rather to keep it from growing. If we remove that foot from the brake, we may prolong time to progression but perhaps not prevent recurrence or change overall survival." ■

— Kathy D Miller, MD
Breast Cancer Update Issue 5, 2008

9 Will the combination or sequence of lapatinib and trastuzumab provide superior survival benefit compared to lapatinib or trastuzumab alone as adjuvant anti-HER2 therapy for patients receiving (neo)adjuvant chemotherapy?

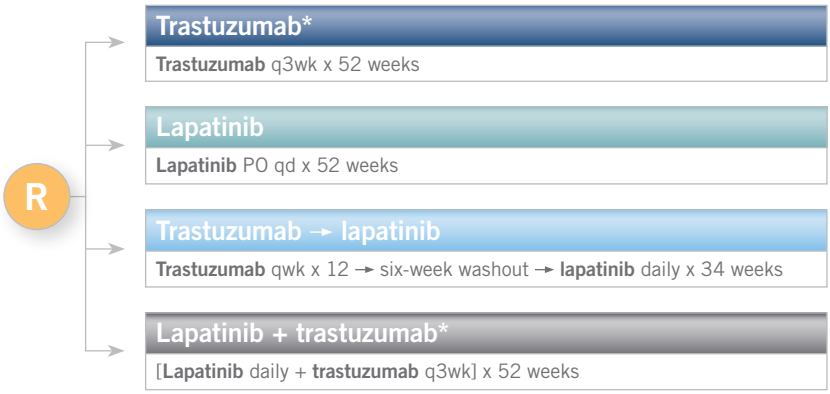
ALTTO (BIG 2-06)

A randomized, multicenter, open-label, Phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2-positive primary breast cancer

TRIAL DESIGN

In Design 1, patients will complete all (neo)adjuvant chemotherapy before administration of targeted therapy.

In Design 2, patients will receive weekly paclitaxel concurrently for 12 weeks with targeted therapy after any anthracycline-based (neo)adjuvant chemotherapy.



* Design 2: Trastuzumab qwk for first 12 weeks, then at q3wk intervals, if continued

KEY FACTS

Select Eligibility Criteria

- Primary invasive breast carcinoma
- Adequate tumor excision and axilla dissection (if positive sentinel node)
- Axillary node-positive or node-negative with tumor ≥ 1 cm (≥T1c)
- Known ER or ER/PR status
- HER2-positive (IHC 3+, IHC 2+ and FISH/CISH amplification, amplification by FISH/CISH of >2.2)
- No prior use of anti-HER2 therapy
- Baseline LVEF ≥ 50%

Stratification

- cMYC gene amplification
- Expression levels of PTEN
- p95HER2 domain

Primary Endpoint

- Compare disease-free survival (DFS) between each of the lapatinib-containing arms and the trastuzumab-alone arm

Secondary Endpoints

- Overall survival
- Time to recurrence
- Time to distant recurrence
- Safety and tolerability
- Cumulative incidence of brain metastases as the first site of breast cancer recurrence

Target Accrual: 8,000

Date Activated: June 2007

Estimated Completion Date: June 2010

Study Contacts

Breast International Group
Email: ALTTOtrials@bordet.be
North Central Cancer Treatment Group
Email: altto@mayo.edu
GlaxoSmithKline
Email: lapatinibtrials.northamerica@gsk.com
ClinicalTrials.gov Identifier: NCT00490139

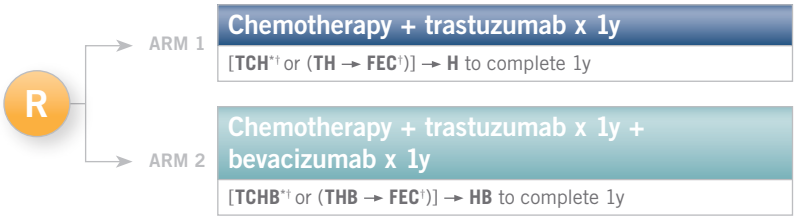
SOURCES: NCI Physician Data Query, October 2008; www.alttotrials.com; www.clinicaltrials.gov.

10 Does the addition of bevacizumab to adjuvant chemotherapy and trastuzumab improve disease-free survival in node-positive or high-risk node-negative, HER2-positive early breast cancer?

NSABP/CIRG BETH

Chemotherapy and trastuzumab with or without bevacizumab as treatment for patients with HER2-positive early breast cancer

TRIAL DESIGN



T = docetaxel; C = carboplatin; H = trastuzumab; FEC = 5-FU, epirubicin, cyclophosphamide; B = bevacizumab (15 mg/kg IV d1 q3wk)

* Chemotherapy used by NSABP/CIRG investigators (Cohort 1)

† Chemotherapy used by independent investigators (Cohort 2)

KEY FACTS

Select Eligibility Criteria

- Node-positive or high-risk, node-negative
- HER2-positive by central FISH and/or IHC 3+ testing
- LVEF ≥ 55%

Stratification

- Nodal status
- Hormone receptor status

Primary Endpoint

- Invasive disease-free survival

Secondary Endpoints

- Disease-free survival, overall survival, recurrence-free survival, distant recurrence-free survival, toxicity, biomarker identification

Target Accrual: 3,500

Date Activated: June 2008

Estimated Completion Date: June 2012

Study Contacts

NSABP
Norman Wolmark, MD, Principal Investigator
Diana Gosik, RN, BS
Tel: 412-330-4692
Email: diana.gosik@nsabp.org

Cancer International Research Group
Tel: +1-780-702-0189
E-mail: contact@cirg.org

ClinicalTrials.gov Identifier: NCT00625898

SOURCES: NCI Physician Data Query, October 2008; **www.nsabp.pitt.edu**; **www.bcirg.org**.

"We know that HER2 is an upstream regulator of VEGF production. That has been shown definitively both in cell lines and in the clinic. A woman who has HER2-positive breast cancer simply has more VEGF in her tumor. In some lovely preclinical modeling that was presented in *Nature* a few years ago, the HER2-positive tumors were considerably more vascular than the HER2-negative tumors. From a clinical standpoint, these tumors have a higher microvessel density. More importantly, VEGF expression is a clear regulator of outcome. In a study conducted by Gottfried Konecny at UCLA, the tumors with the worst performance were the ones that were both HER2-positive and VEGF-positive, so that combination of HER2 positivity and VEGF overexpression appears to be clinically important." ■

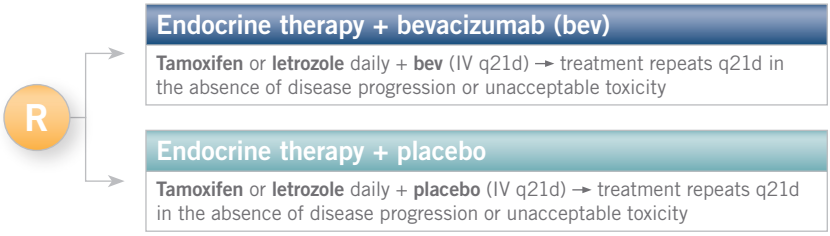
— George W Sledge Jr, MD
Breast Cancer Update Issue 6, 2007

11 Will the addition of bevacizumab to endocrine therapy improve outcomes for patients with ER/PR-positive advanced disease?

CALGB-40503

Endocrine therapy in combination with anti-VEGF therapy: A randomized, double-blind, placebo-controlled Phase III trial of endocrine therapy alone or endocrine therapy with bevacizumab for women with ER/PR-positive advanced breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Female
- Inoperable, locally advanced or metastatic breast cancer
- Postmenopausal (ovarian ablation required if premenopausal)
- No known CNS metastases, recent thrombolic events, significant proteinuria (must demonstrate <1g/24hr), uncontrolled hypertension, history of DVT or PE, major surgery within the last four weeks or serious nonhealing wound or bone fracture
- ER-positive and/or PR-positive
- Measurable or nonmeasurable disease by RECIST
- ECOG PS 0-1
- Prior endocrine therapy in the adjuvant setting allowed
- No prior anti-VEGF or VEGFR tyrosine kinase inhibitor therapy

Stratification

- Letrozole versus tamoxifen
- Measurable versus nonmeasurable disease
- Disease-free interval from initial diagnosis to first progression (≤24mo versus >24mo)

Primary Endpoints

- Progression-free survival (defined as the interval from randomization to disease progression or death, whichever occurs first, in patients treated with letrozole)
- Estimation of adverse events rate (especially for stroke, proteinuria, thrombosis and hypertension, in patients treated with tamoxifen)
- Toxicity

Secondary Endpoints

- Objective tumor response (as defined by RECIST for patients with measurable disease)
- Probability of being progression free at six and 12 months
- Site of progression
- Treatment-related toxicity
- Time to treatment failure
- Duration of tumor response
- Overall survival
- Probability of surviving until 36 months

Target Accrual: 502

Date Activated: May 2008

Estimated Completion Date: February 2009

Study Contact

Cancer and Leukemia Group B
Maura N Dickler, MD, Principal Investigator
Tel: 800-525-2225

ClinicalTrials.gov Identifier: NCT00601900

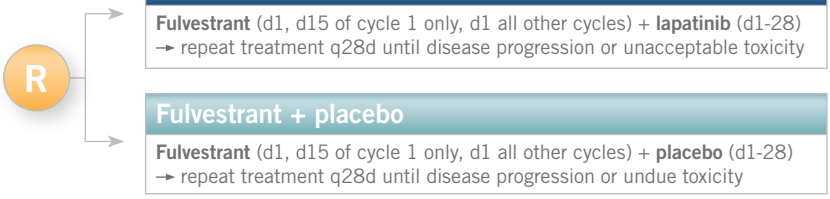
SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov; www.ctsu.org.

12 Does lapatinib add benefit to fulvestrant for postmenopausal women with advanced disease?

CALGB-40302

Endocrine therapy with or without inhibition of EGF and HER2 growth factor receptors: A randomized, double-blind, placebo-controlled Phase III trial of fulvestrant with or without lapatinib for postmenopausal women with ER/PR-positive advanced breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Primary or metastatic Stage IV or locally advanced Stage III breast cancer
- Postmenopausal
- No active CNS metastasis
- ER-positive and/or PR-positive
- HER2 status known
- At least one measurable lesion or bone metastasis
- Prior aromatase inhibitor treatment
- No prior trastuzumab for metastatic breast cancer
- No prior fulvestrant or EGFR inhibitor

Stratification

- Prior tamoxifen (yes/no)
- Bone disease only (yes/no)

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Treatment-related toxicity
- Objective tumor response as defined by RECIST
- Duration of tumor response
- Overall survival
- Quality of life as measured by Memorial Symptom Assessment Scale

Target Accrual: 324

Date Activated: September 2006

Estimated Completion Date: December 2008

Study Contact

Cancer and Leukemia Group B
Harold J Burstein, MD, PhD, Protocol Chair
Tel: 866-790-4500
Email: hburstein@partners.org

ClinicalTrials.gov Identifier: NCT00390455

SOURCES: www.clinicaltrials.gov; www.ctsu.org.

"The CALGB 40302 trial is an ongoing study for ER-positive breast cancer, in which patients with metastatic disease receive fulvestrant with or without lapatinib. It is open to patients with both HER2-positive and HER2-negative disease. Our goal is to determine whether dual inhibition of the ER and HER2 pathways is beneficial to either HER2-positive or HER2-negative tumors.

For the moment in HER2-positive metastatic disease, first-line therapy is trastuzumab with chemotherapy. We have compelling survival data for that. Second-line options include ongoing trastuzumab with the chemotherapy of your choice. At some point, one introduces lapatinib. I believe that it's difficult to be dogmatic about when that moment should be." ■

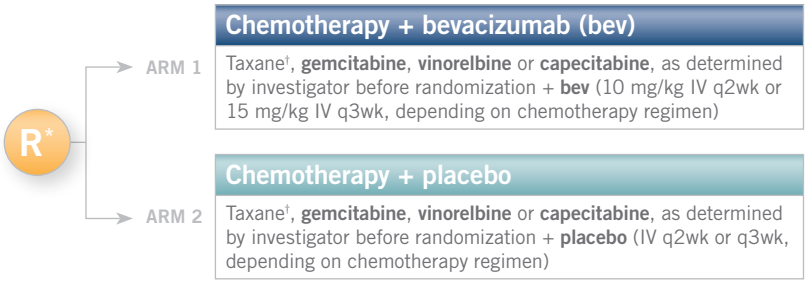
— Harold J Burstein, MD, PhD
Year in Review — A Daylong CME Symposium Focused on Key Clinical Presentations and Papers in Oncology: 2007-2008

13 Does bevacizumab add benefit to chemotherapy for patients with previously treated metastatic breast cancer?

RIBBON 2 (AVF3693g)

A Phase III, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously treated metastatic breast cancer

TRIAL DESIGN



* 2 to 1 randomization of Arm 1 to Arm 2
† Docetaxel, paclitaxel or *nab* paclitaxel

KEY FACTS

Select Eligibility Criteria

- Metastatic breast cancer
- Progression of disease during or after administration of one chemotherapy regimen administered in the first-line setting
- ECOG PS 0 or 1
- No unknown or HER2-positive disease
- No unknown ER or PR status
- For those who received prior anthracycline-based therapy: LVEF ≥ 50% by MUGA or ECHO
- No NYHA Grade II or greater CHF
- No history of myocardial infarction within the past six months
- No brain or CNS metastases
- No history of stroke or TIA within the past six months
- No clinically significant peripheral vascular disease
- No evidence of bleeding diathesis or coagulopathy
- No history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within the past six months
- No serious nonhealing wound, ulcer or bone fracture
- No major surgical procedure within the past 28 days

Stratification

- Chemotherapy regimen
- Interval from time of diagnosis
- Number of metastatic sites

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall survival
- Objective response rate
- Duration of objective response
- Safety
- One-year survival

Target Accrual: 650

Date Activated: February 2006

Estimated Completion Date: April 2010

Study Contact

Genentech BioOncology
Jai Balkissoon, MD, Study Director
Tel: 888-662-6728

ClinicalTrials.gov Identifier: NCT00281697

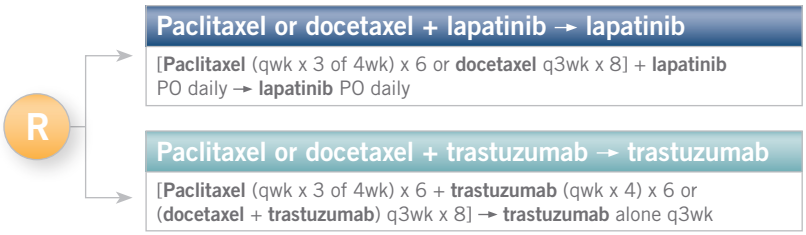
SOURCES: NCI Physician Data Query, October 2008; **www.clinicaltrials.gov**; O'Shaughnessy JA, Brufsky AM. *Clin Breast Cancer* 2008;8(4):370–3. No abstract available

14 Is lapatinib or trastuzumab more effective in combination with a taxane for patients with HER2-positive metastatic breast cancer?

CAN-NCIC-MA31

A Phase III randomized trial of taxane-based chemotherapy with lapatinib versus with trastuzumab for women with HER2-positive metastatic breast cancer

TRIAL DESIGN



Patients complete quality-of-life questionnaires (EORTC QLQ-C30 and a trial-specific checklist) at baseline, every 12 weeks for 96 weeks and then every 24 weeks until disease progression.

Formalin-fixed, paraffin-embedded tissue samples are analyzed for ER, PR, EGFR, CK5/6, Ki-67 and other molecular biomarkers by tissue microarray and immunohistochemistry.

KEY FACTS

Select Eligibility Criteria

- Stage IV HER2-overexpressing and/or amplified breast cancer (invasive tumor cells with IHC 3+ in >30%, IHC 2+ or 3+ in ≤30% and demonstration of HER2 gene amplification by FISH, or HER2 gene amplification by FISH)
- Availability of formalin-fixed, paraffin-embedded tumor specimens
- No CNS metastases (including leptomeningeal involvement)
- ECOG PS 0-2
- LVEF ≥ 50% by MUGA or ECHO
- ≥12 months since prior chemotherapeutic agents and prior anti-HER2 targeted therapy in the adjuvant or neoadjuvant setting
- No serious cardiac illness or condition, including history of CHF or systolic dysfunction, high-risk uncontrolled arrhythmias, unstable angina, uncontrolled hypertension

Stratification

- Prior neoadjuvant/adjuvant anti-HER2 targeted therapy
- Prior neoadjuvant/adjuvant taxane chemotherapy
- Paclitaxel versus docetaxel
- Presence of liver metastasis

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall survival
- Incidence and time to CNS metastasis at first progression
- Overall objective response rate, time to response and response duration
- Clinical benefit response rate
- Adverse event
- Quality of life
- Clinical outcomes measured by biomarker changes in biological samples
- Economic evaluation

Target Accrual: 600

Date Activated: July 2008

Estimated Completion Date: July 2011

Study Contact

NCIC-Clinical Trials Group
GlaxoSmithKline
Karen Gelmon, MD, Protocol Chair
Tel: 800-663-3333
Email: kgelmon@bccancer.bc.ca

ClinicalTrials.gov Identifier: NCT00667251

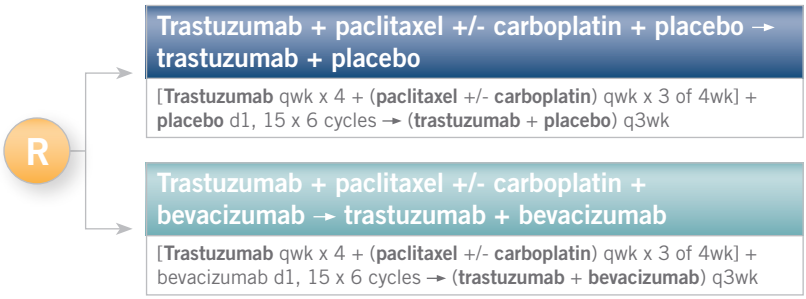
SOURCES: NCI Physician Data Query, October 2008; **www.clinicaltrials.gov**.

15 Does bevacizumab increase the efficacy of first-line trastuzumab with chemotherapy in HER2-positive metastatic breast cancer?

ECOG-E1105

A randomized Phase III trial of first-line chemotherapy and trastuzumab with or without bevacizumab for patients with HER2-overexpressing metastatic breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Histologically confirmed HER2 overexpression (IHC 3+ or FISH+)
- Men and women
- Metastasis and/or chest wall recurrence
- Measurable or nonmeasurable evaluable disease confirmed
- No evidence of CNS disease
- ECOG PS 0-1
- INR ≤ 1.5 X ULN; PTT ≤ 1.5 X ULN
- LVEF > LLN by MUGA or ECHO
- No Grade II, III or IV neuropathy
- No clinically significant cardiovascular disease
- No current nonhealing wound or fracture
- Adjuvant trastuzumab ≥ 12 months before recurrence

Stratification

- Prior treatment with adjuvant trastuzumab
- Prior treatment with neoadjuvant or adjuvant taxane
- Disease-free interval (>24mo versus ≤24mo)
- Planned treatment with carboplatin

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall survival
- Response rates
- Time to progression
- Six-month progression-free survival
- Toxicity
- Comparison of breast cancer symptoms with treatment-related symptoms

Target Accrual: 489

Date Activated: November 2007

Estimated Completion Date: November 2009

Study Contacts

Eastern Cooperative Oncology Group
Ingrid Mayer, MD, Protocol Chair
Carlos L Arteaga, MD, Protocol Co-chair
Tel: 800-811-8480
Email: carlos.arteaga@vanderbilt.edu
North Central Cancer Treatment Group
Edith A Perez, MD, Protocol Chair
Tel: 866-790-4500
Cancer and Leukemia Group B
Nancy Lin, MD, Protocol Chair
Tel: 866-790-4500
Southwest Oncology Group
Mohammad Jahanzeb, MD, Protocol Chair
Tel: 901-722-0532

ClinicalTrials.gov Identifier: NCT00520975

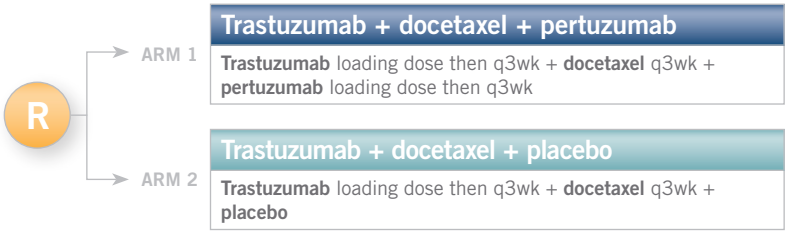
SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov.

16 Will pertuzumab combined with trastuzumab and chemotherapy improve outcomes for patients with newly diagnosed HER2-positive metastatic breast cancer?

CLEOPATRA

A Phase III, double-blind trial to evaluate the efficacy and safety of trastuzumab and docetaxel with or without pertuzumab in previously untreated HER2-positive metastatic breast cancer

TRIAL DESIGN



Treatment continues in both arms until disease progression or unmanageable toxicity.

KEY FACTS

Select Eligibility Criteria

- Locally recurrent or metastatic breast cancer
- HER2-positive (FISH-positive or IHC 3+)
- Baseline LVEF ≥ 50% within 42 days of randomization
- ECOG PS 0-1
- No prior therapy for metastatic breast cancer (one prior hormonal regimen allowed)
- No prior therapy with tyrosine kinase/HER inhibitors for breast cancer, except neoadjuvant or adjuvant trastuzumab
- No neoadjuvant or adjuvant therapy with <12-month disease-free interval between treatment completion and metastatic diagnosis
- No CNS metastases
- No uncontrolled hypertension or unstable angina
- No current known infection with HIV, HBV or HCV
- No myocardial infarction within six months of randomization
- No clinically relevant cardiovascular disease

Primary Endpoint

- Progression-free survival by independent review

Secondary Endpoints

- Overall survival
- Time to symptom progression
- Objective response
- Cardiac function
- Adverse events and serious AEs
- Laboratory abnormalities

Target Accrual: 800

Date Activated: February 2008

Estimated Completion Date: March 2012

Study Contact

Hoffman-La Roche
Virginia Paton, PharmD, Study Director
Tel: 888-662-6728, Ext. 4
ClinicalTrials.gov Identifier: NCT00567190

SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov; Roche Clinical Trials Registry, October 2008.

17 What is the efficacy and safety of pazopanib when combined with lapatinib for HER2-positive, metastatic, inflammatory breast cancer?

VEG108838

A randomized Phase III trial comparing pazopanib and lapatinib versus lapatinib monotherapy in patients with HER2-overexpressing inflammatory breast cancer

TRIAL DESIGN

KEY FACTS

Select Eligibility Criteria

- Clinical diagnosis of inflammatory breast cancer (IBC) with histological confirmation
- Disease progression or relapse following treatment which included chemotherapy or chemotherapy with trastuzumab, where available
- HER2 overexpression (local results of IHC 3+ or FISH- or CISH-positive). Archived tumor tissue must be available from all patients for central laboratory testing. Patients remain on study based on local HER2 expression results
- Radiographically measurable disease according to RECIST or evaluable IBC cutaneous disease. Cutaneous disease must have been biopsied at some time, if that is the only evidence of recurrent IBC
- Radiographically measurable lesions may be in the field of prior adjuvant irradiation, but there must be at least an eight-week period between the last radiation and baseline scan documenting disease status. If the irradiated lesion is the only site of disease, documented progression of the irradiated lesion is required
- Adequate organ function
- Cardiac ejection fraction by echocardiogram must be within normal range. MUGA scans accepted where an echocardiogram cannot be performed or is inconclusive or where MUGA scans are the accepted standard
- No history of uncontrolled or symptomatic angina, arrhythmia or congestive heart failure
- ECOG PS 0-2
- No prior lapatinib therapy
- No history or clinical evidence of CNS metastases or leptomeningeal carcinomatosis
- No clinically significant gastrointestinal abnormalities that may increase risk of GI bleeding
- No history of cardiovascular conditions within six months including angioplasty or stenting, myocardial infarction, unstable angina, poorly controlled hypertension and Class III or IV congestive heart failure

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall response rate
- Overall survival
- Safety and tolerability

Target Accrual: 320

Date Activated: December 2007

Estimated Completion Date: May 2010

Study Contact

US GSK Clinical Trials Call Center
Tel: 877-379-3718

ClinicalTrials.gov Identifier: NCT005558103

SOURCE: www.clinicaltrials.gov.

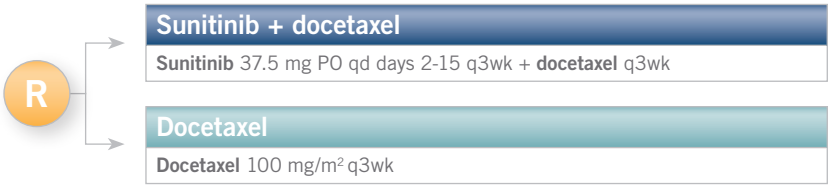
"Pazopanib (GW786034) is a second-generation multitargeted tyrosine kinase inhibitor against vascular endothelial growth factor receptor-1, -2, and -3, platelet-derived growth factor receptor-alpha, platelet-derived growth factor receptor-beta, and c-kit. Preclinical evaluation has revealed excellent antiangiogenic and antitumor activity, and synergism was observed in combination with chemotherapeutic drugs. Phase I clinical trials have revealed manageable toxicities and desirable pharmacokinetics as well as activity in renal cancer and several other tumors. Ongoing trials are further evaluating pazopanib in a variety of malignancies." ■

— Sonpavde G, Hutson TE. *Curr Oncol Rep* 2007;9:115-9.

18 Is sunitinib combined with docetaxel more efficacious than docetaxel alone for patients with advanced breast cancer?

SUN 1064 — A randomized Phase III study of docetaxel in combination with sunitinib versus docetaxel as first-line treatment for patients with advanced breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Age ≥ 18
- Women
- Unresectable locally recurrent or metastatic breast cancer
- ECOG PS 0 or 1
- Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) or bone-only disease
- HER2-negative
- Excludes inflammatory carcinoma with no other measurable disease
- No patients for whom docetaxel is contraindicated
- No treatment with an adjuvant taxane within the past 12 months
- No prior treatment with chemotherapy in the metastatic disease setting or with sunitinib malate
- No major surgery or systemic therapy (with the exception of hormone therapy) within the past three weeks
- No brain metastases, spinal cord compression, carcinomatous meningitis or leptomeningeal disease
- None of the following within the past six months: myocardial infarction, severe/unstable angina, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus

Stratification

- Number of metastatic organ systems
- Estrogen receptor status
- Disease-free interval from prior adjuvant treatment

Primary Endpoint

- Progression-free survival — radiographic progression of disease

Secondary Endpoints

- Overall response rate
- Duration of response
- Overall survival
- Patient-reported outcomes
- Safety

Target Accrual: 550

Date Activated: February 2007

Estimated Completion Date: November 2011

Study Contacts

Pfizer Inc
Director, Clinical Trial Resource Group
Information Service
Tel: 877-369-9753
Pfizer CT.gov Call Center
Tel: 800-718-1021

ClinicalTrials.gov Identifier: NCT00393939

SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov; www.suntrials.com.

19 Is the multitargeted tyrosine kinase inhibitor sunitinib with paclitaxel superior to bevacizumab with paclitaxel as front-line therapy for advanced breast cancer?

A6181094 — A Phase III study of sunitinib in combination with paclitaxel versus bevacizumab with paclitaxel in the first-line advanced disease setting in patients with breast cancer

TRIAL DESIGN

KEY FACTS

Select Eligibility Criteria

- Advanced breast cancer
- Measurable disease as per RECIST or bone-only disease
- ECOG PS 0 or 1
- No prior treatment with cytotoxics in the advanced disease setting
- No HER2-positive disease unless patient previously experienced progression on prior treatment with trastuzumab
- No treatment with a taxane in the adjuvant setting unless disease-free interval > 12 months after end of treatment
- No bevacizumab or sunitinib malate in the advanced disease setting
- No myocardial infarction, severe/unstable angina, CHF, cerebrovascular accident, pulmonary embolus, DVT or other significant thromboembolic events within the past six months

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Objective response rate, duration of response, overall survival, two- and three-year survival, patient-reported outcomes, biomarkers, safety

Target Accrual: 740

Date Activated: November 2006

Estimated Completion Date: May 2010

Study Contacts

Pfizer Inc
Director, Clinical Trial Resource Group
Information Service
Tel: 877-369-9753
Pfizer CT.gov Call Center
Tel: 800-718-1021

ClinicalTrials.gov Identifier: NCT00373256

SOURCES: NCI Physician Data Query, October 2008; www.clinicaltrials.gov.

"Sunitinib (SU011248) is an oral small molecular tyrosine kinase inhibitor that exhibits potent antiangiogenic and antitumor activity. . . [S]unitinib was rationally designed and chosen for its high bioavailability and its nanomolar-range potency against the antiangiogenic receptor tyrosine kinases (RTKs) — vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Sunitinib inhibits other tyrosine kinases including, KIT, FLT3, colony-stimulating factor 1 (CSF-1), and RET, which are involved in a number of malignancies...

Studies investigating sunitinib alone in various tumor types and in combination with chemotherapy are ongoing. The clinical benchmarking of this small-molecule inhibitor of members of the split-kinase domain family of RTKs will lead to additional insights regarding the biology, potential biomarkers, and clinical utility of agents that target multiple signaling pathways in tumor, stromal, and endothelial compartments." ■

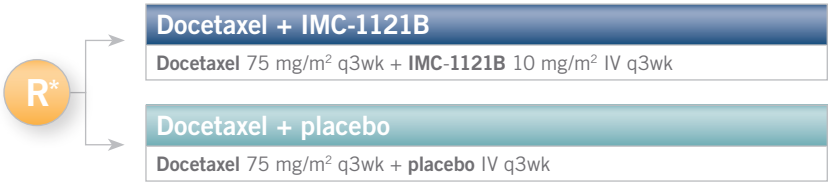
— Chow LQ, Eckhardt SG.
J Clin Oncol 2007;25:884-96.

20 What is the efficacy and safety of a novel anti-angiogenic agent targeting VEGFR-2 with docetaxel in the treatment of metastatic breast cancer?

TRIO-012, CP12-0606

A multicenter, multinational, randomized, double-blind, Phase III study of IMC-1121B (a fully humanized monoclonal antibody targeting VEGFR-2) and docetaxel versus placebo and docetaxel in previously untreated patients with HER2-negative, unresectable, locally-recurrent or metastatic breast cancer

TRIAL DESIGN



* 2 to 1 randomization to docetaxel + IMC-1121B versus docetaxel + placebo

Treatment will continue until there is evidence of progressive disease, unacceptable toxicity or other withdrawal criteria are met. Patients who discontinue study treatment with either IMC-1121B or placebo may continue to receive docetaxel. Similarly, patients who discontinue docetaxel therapy may continue to receive either IMC-1121B or placebo, whichever the patient was randomized to receive. All patients will be followed for survival at regularly scheduled intervals (every six weeks until progressive disease and every six months thereafter) for at least 36 months after discontinuing study therapy.

KEY FACTS

Select Eligibility Criteria

- Unresectable, locally recurrent or metastatic breast cancer
- Measurable and/or nonmeasurable disease
- HER2-negative via FISH, CISH or IHC 0, 1+
- No prior chemotherapy for metastatic or locally-recurrent, inoperable breast cancer
- LVEF within normal institutional range
- Adequate coagulation function
- ECOG PS 0-1

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall survival
- Time to progression
- Overall response rate
- Response duration
- Quality of life
- Safety
- Immunogenicity of IMC-1121B

Exploratory Endpoints

- Calculate the change in circulating tumor cells
- Analyze VEGFR polymorphisms
- Assess tumor tissue samples for potential markers of therapeutic efficacy and/or safety
- Explore the effect of genetic variation on therapeutic efficacy and/or safety

Target Accrual: 1,113

Date Activated: June 2008

Estimated Completion Date: June 2012

Study Contacts

Cancer International Research Group
John Mackey, MD, Principal Investigator
Francois Thireau
Tel: 33 1 58 100915
Email: francoisthireau@cirg.org

ClinicalTrials.gov Identifier: NCT00703326

SOURCES: www.clinicaltrials.gov; www.bcirg.org.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **NSABP-B-40 is a neoadjuvant trial of three chemotherapy regimens with or without _____.**
   a. Trastuzumab
   b. Lapatinib
   c. Bevacizumab
2. **In the NSABP neoadjuvant study B-41 evaluating AC followed by paclitaxel in combination with anti-HER2 therapy for patients with operable HER2-positive breast cancer, paclitaxel is administered _____.**
   a. Weekly
   b. Every two weeks
   c. Every three weeks
3. **In the neoadjuvant studies for operable HER2-positive breast cancer — NSABP-B-41, ACOSOG-Z1041 and the Neo-ALTTO trial — patients will receive postoperative adjuvant anti-HER2 therapy.**
   a. True
   b. False
4. **Both the NSABP-B-41 and the Neo-ALTTO neoadjuvant studies for operable HER2-positive breast cancer will evaluate chemotherapy in combination with trastuzumab/lapatinib.**
   a. True
   b. False
5. **In NSABP-B-45, patients with residual invasive breast cancer after preoperative chemotherapy will be randomly assigned to receive placebo or _____.**
   a. Bevacizumab
   b. Capecitabine
   c. Ixabepilone
   d. Sunitinib
6. **In the BEATRICE trial of standard adjuvant chemotherapy (anthracycline with or without taxane or taxane only) with or without bevacizumab for patients with triple-negative breast cancer, what is the duration of administration for the anti-angiogenic agent?**
   a. One month
   b. Three months
   c. Six months
   d. 12 months
7. **In the US Oncology/NSABP collaborative adjuvant trial, patients will be randomly assigned to which of the following treatments?**
   a. Docetaxel/doxorubicin/cyclophosphamide (TAC)
   b. Docetaxel/cyclophosphamide
   c. Docetaxel/cyclophosphamide and bevacizumab
   d. Both a and c
   e. a, b and c
8. **In the international Phase III ALTTO trial for patients with HER2-positive early breast cancer, which treatment arm does not receive 52 weeks of continuous anti-HER2 therapy?**
   a. Trastuzumab
   b. Lapatinib
   c. Trastuzumab followed by lapatinib
   d. Trastuzumab with concurrent lapatinib
9. **The NSABP/CIRG BETH adjuvant trial for patients with node-positive or high-risk, node-negative, HER2-positive early breast cancer will evaluate chemotherapy/trastuzumab with or without _____.**
   a. Lapatinib
   b. Bevacizumab
   c. Sunitinib
10. **In CALGB-40503, evaluating endocrine therapy with or without bevacizumab for postmenopausal patients with inoperable, locally advanced or metastatic breast cancer, which endocrine therapy will patients be allowed to receive?**
    a. Anastrozole
    b. Letrozole
    c. Tamoxifen
    d. Either a or b
    e. Either b or c
11. **In the RIBBON 2 trial for patients with previously treated metastatic breast cancer, investigators may choose any of the following chemotherapeutic agents to combine with bevacizumab except _____.**
    a. Ixabepilone
    b. Gemcitabine
    c. Vinorelbine
    d. Capecitabine
    e. Taxane (docetaxel, paclitaxel, *nab* paclitaxel)
12. **ECOG-E1105 is evaluating first-line chemotherapy/trastuzumab with or without _____ for patients with HER2-positive metastatic breast cancer.**
    a. Lapatinib
    b. Bevacizumab
    c. Pertuzumab
    d. Sunitinib

Post-test answer key: 1c, 2a, 3a, 4a, 5d, 6d, 7e, 8c, 9b, 10e, 11a, 12b

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Major ongoing Phase III trials of neoadjuvant and adjuvant therapy for patients with HER2-negative and HER2-positive breast cancer . . . 4 3 2 1
- Adjuvant trials combining anti-HER2 and anti-VEGF therapies . . . 4 3 2 1
- NSABP-B-45 trial of sunitinib in patients with residual invasive breast cancer after neoadjuvant chemotherapy . . . 4 3 2 1
- BEATRICE trial incorporating bevacizumab with adjuvant anthracyclines/taxanes for triple-negative breast cancer . . . 4 3 2 1
- Strategies evaluating hormonal therapy with anti-HER2 or anti-VEGF agents for ER/PR-positive metastatic breast cancer . . . 4 3 2 1
- Evaluation of novel multikinase inhibitors with chemotherapy for metastatic breast cancer . . . 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Major ongoing Phase III trials of neoadjuvant and adjuvant therapy for patients with HER2-negative and HER2-positive breast cancer . . . 4 3 2 1
- Adjuvant trials combining anti-HER2 and anti-VEGF therapies . . . 4 3 2 1
- NSABP-B-45 trial of sunitinib in patients with residual invasive breast cancer after neoadjuvant chemotherapy . . . 4 3 2 1
- BEATRICE trial incorporating bevacizumab with adjuvant anthracyclines/taxanes for triple-negative breast cancer . . . 4 3 2 1
- Strategies evaluating hormonal therapy with anti-HER2 or anti-VEGF agents for ER/PR-positive metastatic breast cancer . . . 4 3 2 1
- Evaluation of novel multikinase inhibitors with chemotherapy for metastatic breast cancer . . . 4 3 2 1

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Recall the design of ongoing and planned clinical trials evaluating biologic agents in the adjuvant, neoadjuvant and metastatic treatment of breast cancer . . . 4 3 2 1 N/M N/A
- Explain the key scientific questions and molecular tumor subtypes that are currently being addressed through ongoing breast cancer research efforts . . . 4 3 2 1 N/M N/A
- Appraise the standard and investigational treatment strategies that combine and/or sequence biologic agents with chemotherapy, endocrine therapy and other biologic agents . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

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What additional information or training do you need on the activity topics or other oncology-related topics?

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Educational Assessment and Credit Form (continued)

Additional comments about this activity:

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☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

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Breast Cancer Clinical Trials Resource Guide

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