5 Minute JournalClub

POST-SABCS Issue 4, 2013

A Phase II Study of First-Line Eribulin Mesylate for Locally Recurrent or Metastatic HER2-Negative Breast Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. This unique conference provides many clinicians and scientists from around the world a forum for discussing critical issues in the prevention and management of breast cancer. Therefore, SABCS is targeted by many members of the clinical research community as the optimal time to unveil new clinical data. This creates an environment in which yearly published results from a plethora of ongoing clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes.

Although SABCS currently offers online access to the vast majority of the poster and plenary presentations from the annual meeting, the absence of expert assessment concerning practical applications may yield confusion among community oncologists who are challenged almost daily to appropriately apply a multitude of scientific findings across diverse tumors. Thus, identification of those data sets with immediate or impending relevance to the delivery of quality breast cancer care, in conjunction with professional commentary to address resultant practice ambiguity, may prove vastly beneficial to those physicians who are unable to make the annual pilgrimage to San Antonio. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS, including expert perspectives on how these new evidence-based concepts can and should be incorporated into on- and off-protocol patient care. This activity will assist medical oncologists, radiation oncologists, breast/general surgeons, nurses and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the impact of adjuvant chemotherapy on survival for patients with isolated local and regional recurrence of breast cancer, and apply this information to patient care.
- Assess the benefits and side effects of adding bevacizumab to taxane- or anthracycline-based chemotherapy in the adjuvant setting for triple-negative breast cancer.
- Consider the clinical utility of eribulin mesylate as a treatment option in comparison to capecitabine for patients with previously treated locally advanced or metastatic breast cancer based on recent Phase III trial results.
- Describe the early efficacy and toxicity data from the ongoing trial investigating eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.

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Kimberly L Blackwell, MD
Professor of Medicine
Director, Breast Cancer Program
Duke Cancer Institute
Durham, North Carolina

Advisory Committee: Eisai Inc, Novartis Pharmaceuticals Corporation; Consulting Agreements: Novartis Pharmaceuticals Corporation, Xcenda; Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genomic Health Inc, Novartis Pharmaceuticals Corporation.

Lisa A Carey, MD
Richardson and Marilyn Jacobs Preyer Distinguished Professor for Breast Cancer Research
Chief, Division of Hematology and Oncology
Physician-in-Chief
North Carolina Cancer Hospital
Associate Director for Clinical Research
Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

Advisory Committee, Consulting Agreements and Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Research Support: Genentech BioOncology, GlaxoSmithKline, Sanofi.

Edith A Perez, MD
Deputy Director at Large, Mayo Clinic Cancer Center
Group Vice Chair, Alliance of Clinical Trials in Oncology
Serene M and Frances C Durling Professor of Medicine
Mayo Clinic
Jacksonville, Florida

Contracted Research: Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: April 2013
Expiration date: April 2014

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POST-SABCS Issue 4, 2013

A Practice-Changing Paper on Adjuvant Chemotherapy After Surgical Excision of Local Recurrence and Other San Antonio Highlights

To go directly to slides and commentary for this issue, **click here**.

Last June at ASCO, Dr Sandra Swain presented results from one of the most anticipated trials ever introduced by a generation of clinical scientists focused on adjuvant chemotherapy for breast cancer. NSABP-B-38 was launched in 2004 after the groundbreaking CALGB-9741 study documenting the benefit of dose-dense AC → paclitaxel, and it accrued 4,894 patients in an attempt to determine if that regimen with or without gemcitabine yielded better outcomes than TAC. Perhaps even more striking than the results of this trial (all 3 arms had similar efficacy) was that by the time it matured, much of the research community was indifferent about the outcome, having already diverted its full attention to the new world of targeted and novel agents.

As an enlightened thinker and President of ASCO, Dr Swain may have as much to say about biologically driven cancer therapy as anyone, but when I recently interviewed her for an upcoming audio program, among the fascinating topics we explored was a somewhat unexpected paper from San Antonio that may turn out to be one of the most clinically meaningful data sets on adjuvant chemotherapy in quite some time. **The CALOR trial** was a collaboration between Dr Swain's NSABP and the BIG and IBCSG groups and asked the logical but pretty much unaddressed question of whether patients with a local recurrence in the breast or chest wall who have been rendered clinically disease free by surgical excision would benefit from the addition of "pseudoadjuvant" chemotherapy.

The study demonstrated that physician's choice chemotherapy yielded similar benefits to traditional adjuvant treatment (DFS HR 0.59, $p = 0.0455$; OS HR 0.41, $p = 0.02$), but unfortunately the study was underpowered with a final accrual of 162 patients compared to the original goal of 977. Importantly, most of the benefit was observed in **individuals with ER-negative tumors**, and one wonders if these data will lead to studies of genomic assays like Onco*type* on local recurrence, a practice that NSABP chair Dr Norman Wolmark already utilizes clinically.

Although few breast cancer mavens have adopted Dr Wolmark's next-generation strategy, most — including Dr Swain — have suddenly changed their algorithms and now carefully consider postop chemotherapy for patients with local recurrence. Of course, CALOR wasn't the only interesting and potentially applicable chemo-related data set we saw in San Antonio, and the following help further define what we know and don't know:

301 trial of eribulin versus capecitabine

Eribulin — a sea sponge-derived microtubule inhibitor — entered US practice in 2010 as late-line treatment for metastatic disease and, as is common across all cancer medicine, significant interest developed in potentially moving the agent up in the treatment sequence. At San Antonio we were treated to the results of those efforts in the form of **a major Phase III report** comparing the drug to perhaps the most commonly used cytotoxic after a taxane, capecitabine. Although the hope was that eribulin would show greater efficacy, in fact the findings were generally quite similar except perhaps in patients with ER-negative tumors, for whom a trend was evident favoring eribulin.

To get a sense of what these findings — and those from **a related Phase II SABCS data set with eribulin up front** — mean, we queried the 8 investigators participating in our recent breast cancer think tank. Dr Lisa Carey did a good job capsulizing the perspectives of many in the room by stating, "This was not a disappointment. The study was moving a drug that we all have become comfortable with in the very late-line setting to an earlier setting, and if it is as good as a drug like capecitabine, then it is another option with a totally different toxicity profile. I found this to be a useful study and one that helps with practice."

On the flip side, there was unanimity among the think tank faculty that the exact sequence of these agents is probably not consequential in the long run and often decisions are made based on toxicity, method of administration, patient preferences and convenience. Importantly, however, several investigators stated they sometimes lean more toward capecitabine for older patients with ER-positive, HER2-negative tumors and agents like eribulin for triple-negative disease.

Related to the issue of sequencing multiple agents in the metastatic setting, at our CME satellite symposium in San Antonio, Dr George Sledge stated his belief that chemotherapy is often overused at the end of life and is a key component of "futile care." Although arguments can be made for either side of the issue, this Saturday in Washington DC at the annual Oncology Nursing Society Congress we are going to discuss the case of a 54-year-old woman treated at Dana-Farber who in June 2012 made the difficult decision between going to hospice and taking one more shot at chemo. She ultimately elected to go for fifth-line therapy and experienced a partial remission with minimal toxicity that continues to this time, and the patient was able to spend the summer in Cape Cod watching her grandchildren continue to grow. Which agent

the patient received is not as important as the fact that this case both exemplifies the complexity of Dr Sledge's comment and supports the notion that chemotherapy can and still does play an important role in providing patients with best-quality care.

BEATRICE: Adjuvant chemotherapy/bevacizumab (bev)

At SABCS we saw the first presentation of the **BEATRICE trial** evaluating adjuvant bev with a physician's choice taxane- and/or anthracycline-based regimen in patients with triple-negative disease. Given the diminished recent role of bev in the metastatic setting and the well-publicized failure of the adjuvant trial in colorectal cancer, these negative results were not too surprising. Interestingly, Dr Wolmark is still frustrated that the signal of an impressive reduction in recurrence observed when bev was on board in the NSABP-C-08 colon cancer trial has not been further pursued. BEATRICE, like C-08, used one year of bev, and Norm continues to believe that more benefit would be seen with a greater duration of treatment, although this is not likely to be studied.

Next…The final issue of this SABCS-focused series: Late reports from the first generation of adjuvant trastuzumab trials and other related presentations.

Neil Love, MD
Research To Practice
Miami, Florida

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A Phase II Study of First-Line Eribulin Mesylate for Locally Recurrent or Metastatic HER2-Negative Breast Cancer

Presentation discussed in this issue

Vahdat L et al. **Results of a Phase 2, multicenter, single-arm study of eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract P1-12-02**.

Slides from a presentation at SABCS 2012 and transcribed comments from a recent interview with Lisa A Carey, MD (2/25/13)

Background

- The Phase III EMBRACE study demonstrated a significant survival benefit with eribulin for patients with metastatic breast cancer (mBC) (*Lancet* 2011;377:914).
  - The majority of the women in EMBRACE had HER2-negative disease and had received at least 2 chemotherapeutic regimens.
- The tolerability and positive Phase III findings suggest that eribulin may be beneficial when given earlier in the course of treatment for HER2-negative, advanced breast cancer.
- **Objective:** Evaluate the efficacy and safety of single-agent eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancer.

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

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Phase II Study Design

Eligibility (N = 48)

- Locally recurrent or metastatic HER2-negative BC
- >12 mo neoadjuvant or adjuvant chemotherapy
- >2 wk radiation therapy or endocrine therapy

→ Eribulin mesylate 1.4 mg/m^2, IV days 1, 8 q3wk

Primary endpoint: Objective response rate

Secondary endpoints: Safety, time to first response, duration of response, progression-free survival, quality of life

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

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Best Tumor Responses

Resonse	All (n = 48)	ER+ (n = 35)	Triple-negative (n = 10)
Objective response rate Complete response (CR) Partial response (PR)	27.1% 0 27.1%	28.6% 0 28.6%	30% 0 30%
Stable disease (SD)	47.9%	54.3%	30%
Progressive disease (PD)	22.9%	17.1%	30%
Clinical benefit rate (CR + PR + durable SD)	45.8%	54.3%	30%

- 3 patients with ER-/PR+ disease had no objective response (1 SD, 2 PD)
- Median duration of objective response: 7.4 mo
- Median time to first response: 1.4 mo

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

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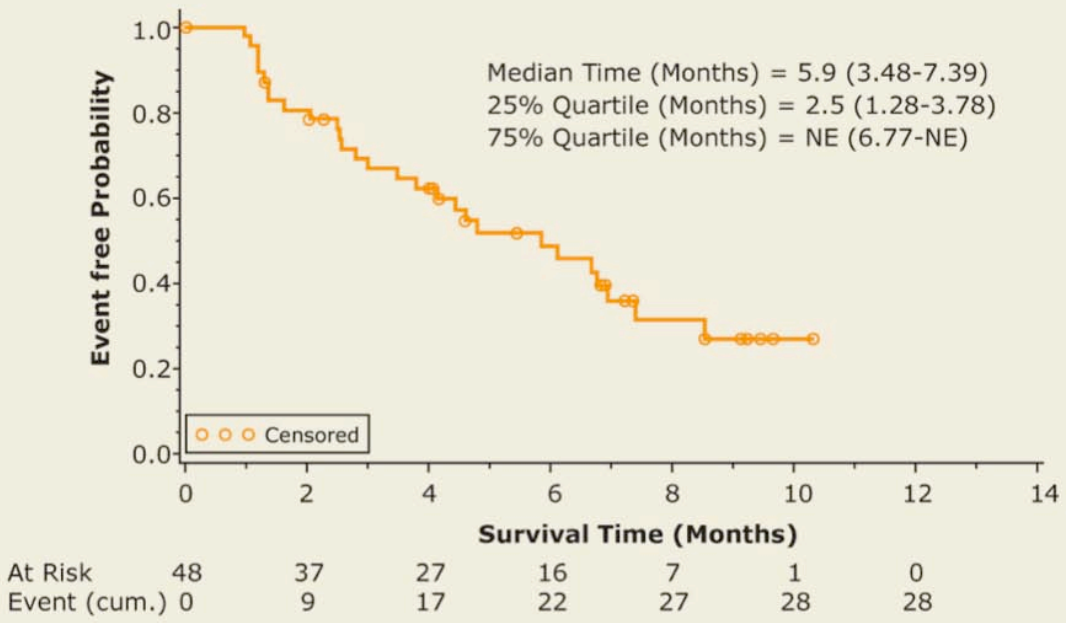
Progression-Free Survival



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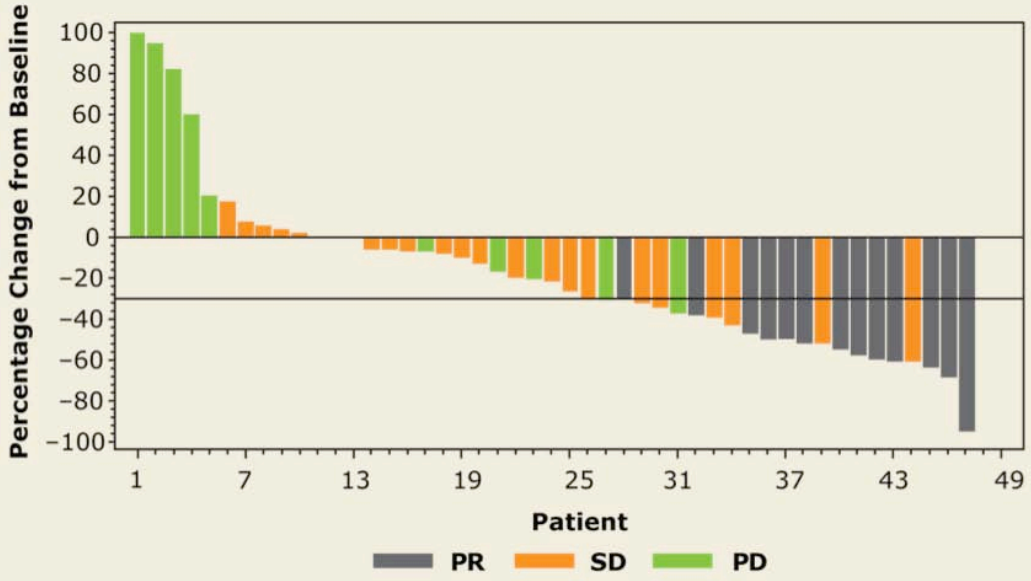
Percentage Change in Total Sum of Target Lesion Diameters from Baseline to Postbaseline Nadir



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Most Common Treatment-Related and Treatment-Emergent (TRTE) Adverse Events (AEs)

AEs (>25% of patients)	All grades (n = 48)	Grade 3/4 (n = 48)
Alopecia	75%	N/A
Neutropenia	72.9%	50%
Fatigue	54.2%	2.1%
Nausea	47.9%	0%
Peripheral neuropathy (PN)	47.9%	12.5%

- Growth factors were administered to 18 (37.5%) patients
- TRTE AEs led to dose adjustment in 26 (54.2%) patients
  - 17 (35.4%) and 20 (41.7%) patients had their dose reduced and delayed, respectively
  - 4 (8.3%) patients discontinued treatment due to an AE (3 due to PN)

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

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Author Conclusions

- The preliminary results of this first-line study suggest that eribulin has antitumor activity in ER+/HER2- and triple-negative metastatic or recurrent breast cancer with an acceptable safety profile. These findings warrant larger studies.
- Alopecia, neutropenia and fatigue were the most common treatment-related adverse events (occurring in >50% of patients).
- The most common Grade 3/4 adverse event was neutropenia, occurring in 50% of patients.
- This study has completed enrollment and final results are expected by the end of 2013.

Vahdat L et al. *Proc SABCS* 2012;Abstract P1-12-02.

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Investigator Commentary: Phase II Study of Eribulin Mesylate as First-Line Therapy for Locally Recurrent or Metastatic HER2-Negative Breast Cancer

This is a preliminary analysis of a single-arm Phase II study of eribulin mesylate as first-line therapy for advanced breast cancer. The data should be interpreted with caution until the final analysis is completed.

About 50 patients with HER2-negative advanced breast cancer received eribulin in the first-line setting. The drug appears to have some activity, with a response rate of about 30% and progression-free survival of approximately 3 to 7 months depending on whether the patients had ER-positive or triple-negative breast cancer.

The usual side effects, such as neutropenia and neuropathy, were seen, but only a few were serious. A differential signal of activity in ER-positive and triple-negative breast cancer was not evident from these data. Without a randomized study, it is not known how eribulin will compare to more conventional agents. However, the PFS with first-line weekly paclitaxel in the CALGB-40502 study was more than 10 months.

Interview with Lisa A Carey, MD, February 25, 2013

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