5 Minute JournalClub

POST-SABCS Issue 4, 2013

A Phase III Trial of Eribulin Mesylate versus Capecitabine for Locally Advanced or Metastatic 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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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.

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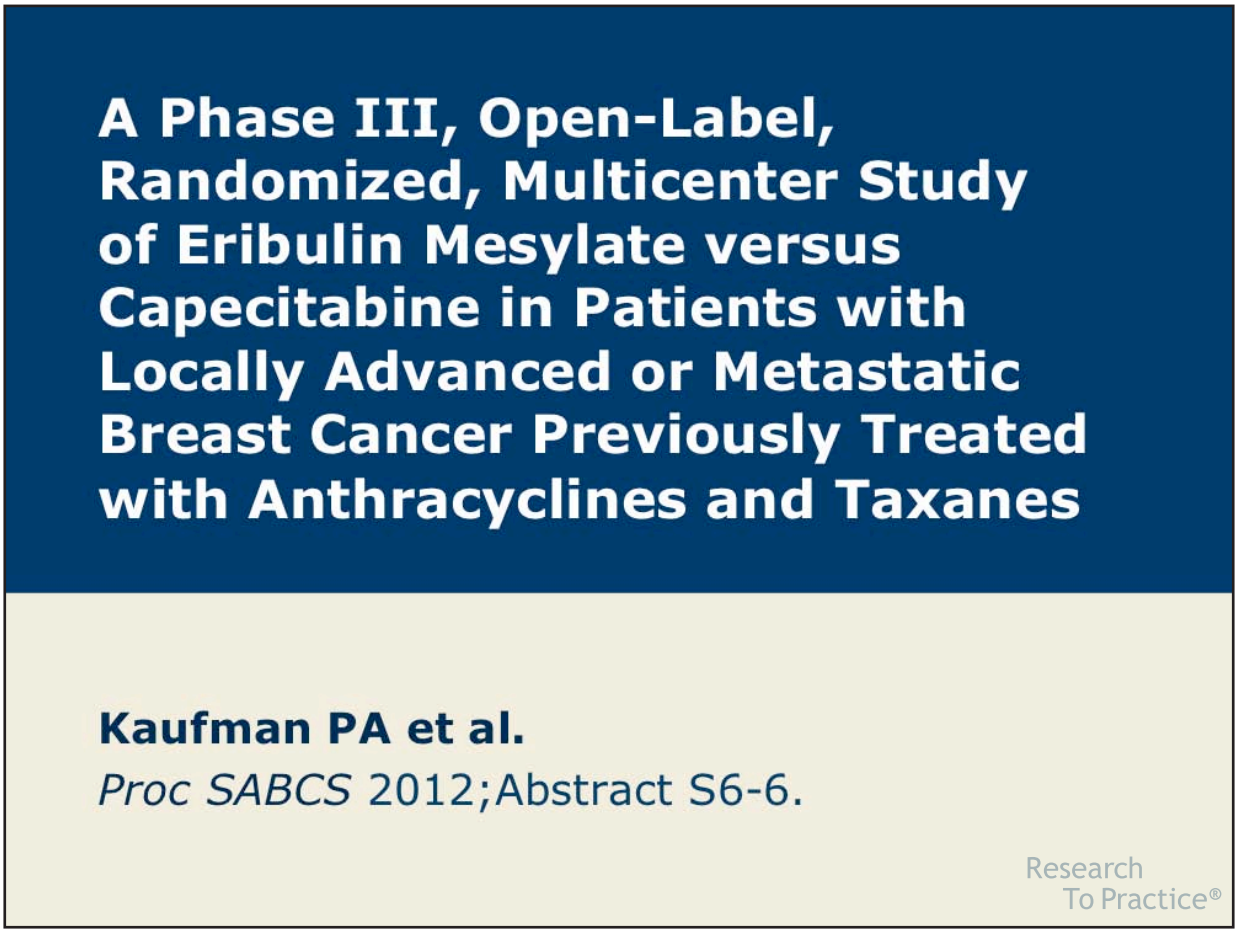
A Phase III Trial of Eribulin Mesylate versus Capecitabine for Locally Advanced or Metastatic Breast Cancer

Presentation discussed in this issue

Kaufman PA et al. **A Phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.** San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

Slides from a presentation at SABCS 2012 and transcribed comments from recent interviews with Kimberly L Blackwell, MD (1/8/13) and Edith A Perez, MD (1/17/13)



Background

- The Phase III EMBRACE trial demonstrated a significant 2.5-month survival advantage with eribulin versus treatment of physician's choice for patients with locally recurrent or metastatic breast cancer (mBC) who previously received ≥2 chemotherapeutic regimens for advanced BC (*Lancet* 2011;377:914).
- Capecitabine is a widely used agent for the treatment of first-, second- and third-line mBC and is approved for mBC that is resistant to paclitaxel and an anthracycline-based regimen.
- **Study objective:** To compare the efficacy and safety of eribulin to capecitabine for patients with locally advanced or mBC previously treated with anthracyclines and taxanes.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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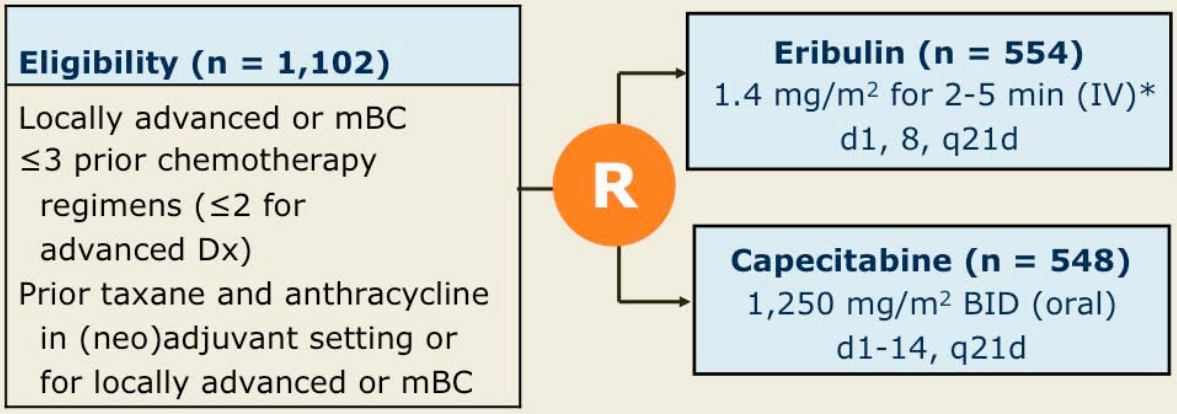
Phase III Study 301 Design



* Equivalent to 1.23 mg/m^2 of eribulin

- **Coprimary endpoints:** Overall survival (OS) and progression-free survival (PFS)
- **Secondary endpoints include:** Quality of life, overall response rate (ORR), duration of response and safety
- Patients were stratified according to geographical region and HER2 status.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Statistical Considerations for Coprimary Endpoints

- Primary predefined analyses for ITT population
  - 2-sided log-rank test, stratified for HER2 and geographic region
  - Hazard ratio (HR) based on Cox regression model
- Planned for enrollment (n = 1,100)
  - OS determination: 905 events
  - Final analysis: 82% of events
  - Sufficient for 90% probability if HR ≤0.8 (Type I error: 0.04)
- 2 planned interim analyses of OS by O'Brien-Fleming spending function: 453 and 603 deaths
- Final analysis would be positive vs capecitabine if either:
  - OS is significantly improved with eribulin ($p \leq 0.0372$)
  - PFS by independent review is significantly prolonged with eribulin ($p \leq 0.01$); HR for OS (eribulin/capecitabine) is <1

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Coprimary Endpoints: OS and PFS

Outcome	Eribulin (n = 554)	Cape (n = 548)	Hazard ratio	*p*-value
Median OS	15.9 mo	14.5 mo	0.879	0.056
1-year OS	64.4%	58.0%	NR	0.035
2-year OS	32.8%	29.8%	NR	0.324
3-year OS	17.8%	14.5%	NR	0.175
Median PFS				
Independent review	4.1 mo	4.2 mo	1.079	0.305
Investigator review	4.2 mo	4.1 mo	0.977	0.736

Cape = capecitabine; NR = not reported

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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OS: Prespecified Subgroup Analysis

Median OS	Eribulin	Cape	Hazard ratio
HER2 status			
Positive	14.3 mo	17.1 mo	0.965
Negative	15.9 mo	13.5 mo	0.838
ER status			
Positive	18.2 mo	16.8 mo	0.897
Negative	14.4 mo	10.5 mo	0.779
Triple-negative BC (TNBC)			
Yes	14.4 mo	9.4 mo	0.702
No	17.5 mo	16.6 mo	0.927
Overall	**15.9 mo**	**14.5 mo**	**0.879**

Hazard ratio <1.0 favors eribulin

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Response Rates

Response	Independent review		Investigator review	
	Eribulin (n = 554)	Cape (n = 548)	Eribulin (n = 554)	Cape (n = 548)
ORR	11%	12%	16%	20%
	p-value = 0.849		*p*-value = 0.100	
SD	57%	55%	60%	51%
PD	23%	24%	18%	23%
NE	2%	1%	6%	6%
Unknown	8%	8%	0%	0%
Unconfirmed CR/PR	—	—	4%	3%
CBR	26%	27%	33%	34%

ORR = objective response rate; SD = stable disease; PD = progressive disease;
NE = not evaluated; CR = complete response; PR = partial response; CBR = clinical benefit rate

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Select Adverse Events (Incidence >10%, All Grades; 1%, Grade 3/4)

Grade	Eribulin (n = 544)		Cape (n = 546)	
	All	3/4	All	3/4
Neutropenia	54%	46%	16%	<5%
Leukopenia	31%	15%	10%	<3%
Febrile neutropenia	2%	<3%	<1%	<2%
Hand-foot syndrome	<1%	0%	45%	14%
Alopecia	35%	—	4%	—
Diarrhea	14%	1%	29%	<6%
Vomiting	12%	<2%	17%	2%
Peripheral sensory neuropathy	13%	4%	7%	<1%
Dyspnea*	10%	<3%	11%	<4%

* Grade 5 events occurred in 0.7% (eribulin) and 0.5% (cape)

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Author Conclusions

- This trial did not demonstrate a statistically significant superiority of eribulin to capecitabine in either OS or PFS.
  - Median OS: 15.9 mo (eribulin), 14.5 mo (cape); HR: 0.879
- Prespecified exploratory analyses suggested that particular patient subgroups may have greater therapeutic benefit with eribulin and this may warrant further study.
  - TNBC (HR: 0.702)
  - ER-negative (HR: 0.779)
  - HER2-negative (HR: 0.838)
- Eribulin and capecitabine demonstrated similar overall activity in this study, which included patients in the first-, second- or third-line treatment setting.
- The toxicity profiles of eribulin and capecitabine were consistent with previously known side effects.

Kaufman PA et al. *Proc SABCS* 2012;Abstract S6-6.

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Investigator Commentary: A Phase III Trial Comparing Eribulin to Capecitabine for Previously Treated Locally Advanced or mBC

In my practice, I'm impressed with eribulin activity. After its approval, I have administered it to patients with heavily pretreated BC. For instance, a patient with PD on every other agent was started on eribulin 9 weeks ago, and her liver lesions have already reduced in size by 50%. Unfortunately, there are no biomarkers to predict response. It was disappointing to discover that eribulin was not superior to capecitabine because it's always good to have a drug that's better than one that's been available for a decade.

Interview with Kimberly L Blackwell, MD, January 8, 2013

This is an important trial for clinical practice. Both eribulin and capecitabine are FDA approved for refractory mBC. This trial showed that eribulin was fairly equivalent to capecitabine in terms of efficacy. Some may view it as a negative study because it failed to demonstrate that eribulin was better than capecitabine. However, I view it as a positive trial showing that there are available options for patients with mBC. The toxic effects for both agents were manageable. Interestingly, in the prespecified subset analysis of patients with TNBC, ER-negative or HER2-negative BC, it appeared that eribulin may offer an advantage over capecitabine. These data support the ongoing evaluation of eribulin in a subset of patients with TNBC.

Interview with Edith A Perez, MD, January 17, 2013