5 Minute JournalClub

Key ASCO Presentations
Issue 5, 2010

Eribulin versus Treatment of Physician's Choice for Patients with Heavily Pretreated Advanced Breast Cancer

For more visit ResearchToPractice.com/5MJCMT2010

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVES

- Recall the Phase III efficacy and safety of eribulin in the clinical management of heavily pretreated advanced breast cancer.
- Identify patients with advanced breast cancer who may benefit from the introduction of eribulin into the treatment algorithm.

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This CME activity contains slides. To receive credit, the participant should review the slide presentation and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

Last review date: July 2010
Expiration date: July 2011

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To go directly to the slides and commentary, **click here**.

The oral sessions on breast cancer in Chicago this year reflected a huge volume of ongoing research, and as usual there were lots of important messages for oncologists in practice, including the following:

1. **Axillary node dissection is on the way out, while intraoperative breast irradiation may be on the way in**
   Several related trial reports were the highlight of one major oral session. The NSABP confirmed what most have believed for years: There is no value in axillary dissection for a patient with a clinically negative axilla and a well-performed negative sentinel node biopsy. Two American College of Surgeons trials demonstrated no prognostic value in IHC staining of H&E-negative sentinel nodes and showed that axillary dissection may not be necessary in all patients with positive sentinel nodes. Finally, the legendary trial champion Mike Baum **proved that** 30 minutes of intraoperative radiation therapy with a $300,000 device may yield comparable results to six weeks of conventional radiation therapy in patients after lumpectomy.

2. **Anti-HER2 therapy continues to gallop along**
   Kathy Miller's early data evaluating the fascinating combination of the chemo/trastuzumab conjugate T-DM1 plus the novel anti-HER2 dimerization inhibitor pertuzumab demonstrated safety, and a related study revealed some possible tissue correlates with efficacy. It's challenging to think of a more creative systemic strategy presented at ASCO.

3. **More of the same and something new for advanced disease**
   Two presentations on bevacizumab/chemotherapy reinforced much of what we already knew. The first, Joyce O'Shaughnessy's presentation of a mini-meta-analysis of first-line bev/chemo trials confirmed the benefit of this agent on progression-free but not overall survival. This seems to be an emerging theme in cancers with long natural histories, as first-line trials often fail to show a survival benefit, whereas studies with patients who have received multiple prior treatments may show a survival advantage, perhaps because of the complexities of post-first-line therapy, including the potential for crossover. Chris Twelves' ASCO data set

demonstrating a survival advantage with the **new antitubulin agent eribulin** is a clear example of this increasingly discussed phenomenon.

In a second presentation addressing anti-angiogenic therapy for advanced breast cancer, Adam Brufsky's reanalysis of the second-line RIBBON 2 trial demonstrated what most believed already: The impact of bev seems relatively independent of its chemo partner.

Next up on 5-Minute Journal Club: The once-mighty imatinib gets another shove out the door with new data on dasatinib, nilotinib and bosutinib in CML.

Neil Love, MD
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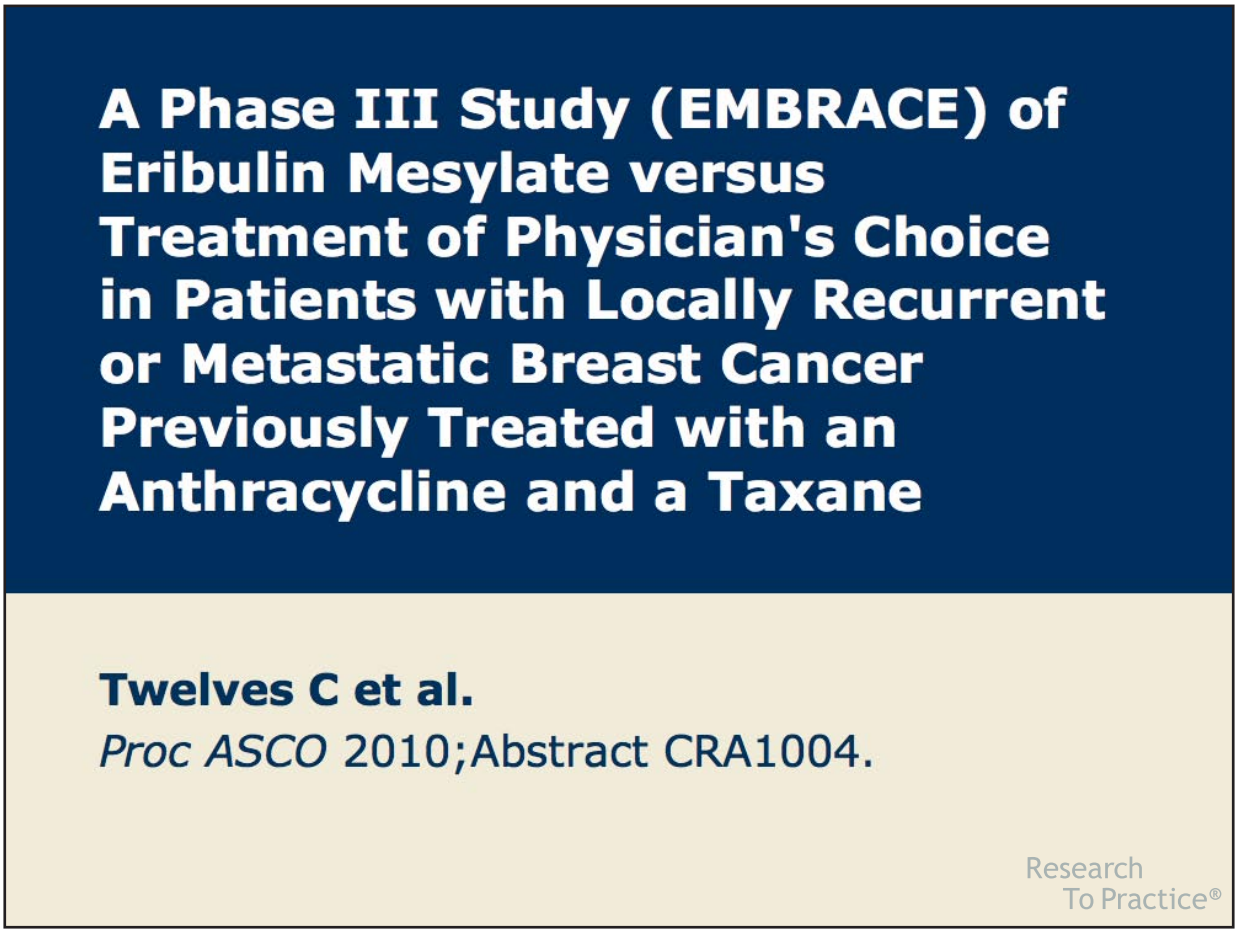
Eribulin versus Treatment of Physician's Choice for Patients with Heavily Pretreated Advanced Breast Cancer

Presentation discussed in this issue

Twelves C et al. **A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane.** *Proc ASCO* 2010;**Abstract CRA1004**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Adam M Brufsky, MD, PhD (6/18/10) and Linda T Vahdat, MD (6/5/10)



Introduction

- No single standard of care treatment exists for heavily pretreated metastatic breast cancer (mBC) and no single agent has demonstrated an overall survival benefit.
- Eribulin mesylate is a synthetic analog of halichondrin B, a natural marine sponge product.
  - Non-taxane microtubule dynamics inhibitor with a novel mode of action
  - Potent anti-proliferative agent in vitro and in vivo
  - Active against β-tubulin mutated cell lines
  - Wide therapeutic window and induces less neuropathy in mice than paclitaxel
  - Overall response rate in heavily pretreated mBC (median prior treatments = 4): 9-12% (ASCO 2008;Abstract 1084; *JCO* 2009;27:2954)
- **Current study objective:**
  - Evaluate eribulin versus treatment of physician's choice in patients with mBC previously treated with an anthracycline and taxane.

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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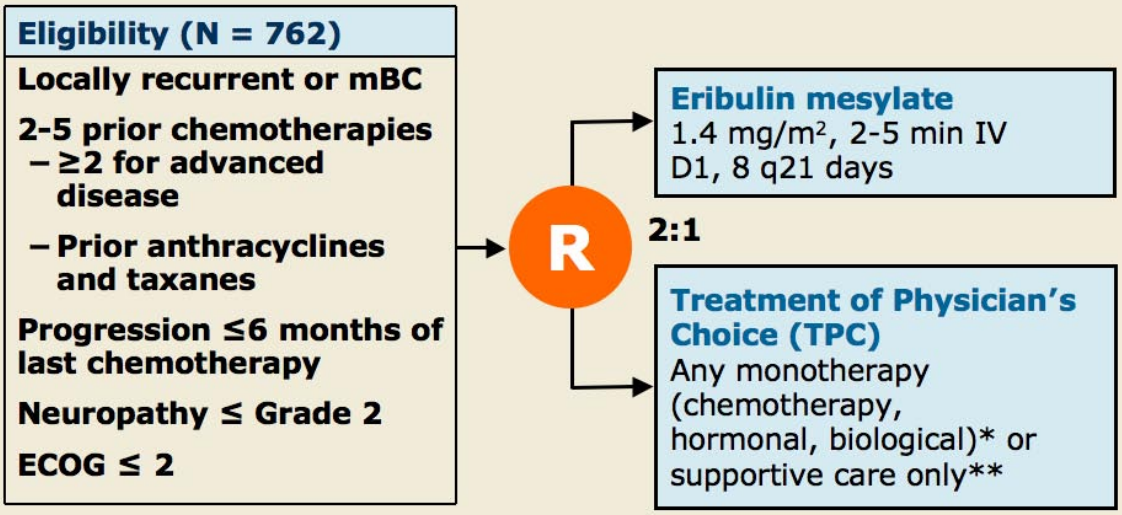
EMBRACE Study Design



* Approved for cancer treatment
** Or palliative treatment or radiotherapy according to local practice

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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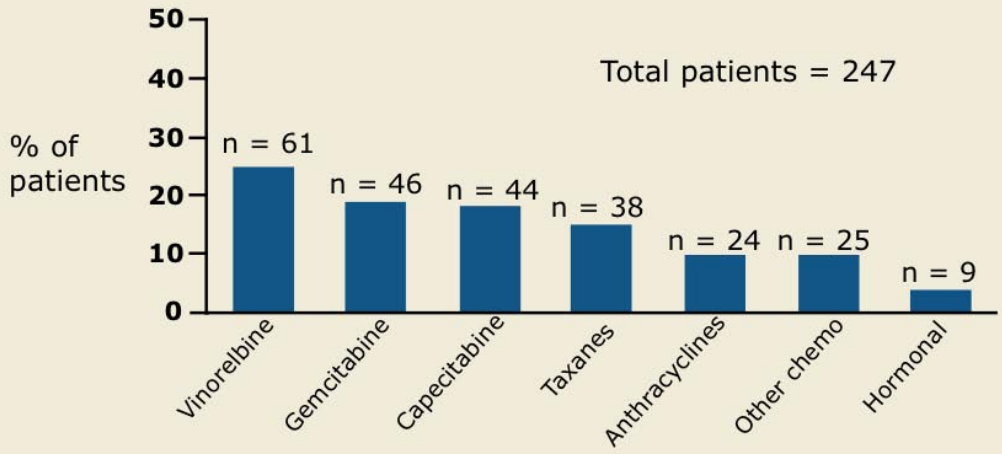
TPC Treatment Received ITT Population

96% of patients treated with chemotherapy



No patient received best supportive care or "biological" therapies only

Taxanes: paclitaxel, docetaxel, nanoparticle albumin-bound (*nab*) paclitaxel; Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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Summary of Efficacy

Endpoint	Eribulin	TPC	Hazard ratio	*p*-value
OS (n = 508, 254)	13.12 mo	10.65 mo	0.81	0.041
PFS* (n = 508, 254)				
Independent review (ITT)	3.7 mo	2.2 mo	0.87	0.14
Investigator review (ITT)	3.6 mo	2.2 mo	0.76	0.002
ORR (CR+PR) (n = 468, 214)				
Independent review (ITT)	12.2%	4.7%	—	0.002
Investigator review (ITT)	13.2%	7.5%	—	0.028
CBR (CR+PR+SD) (n = 468, 214)				
Independent review (ITT)	22.6%	16.8%	—	—
Investigator review (ITT)	27.8%	20.1%	—	—

* PFS in per-protocol population was significant for independent ($p = 0.02$) and investigator ($p < 0.001$) reviews

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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Overall Incidence of Adverse Events

Adverse Event (AE)	Eribulin (n = 503)	TPC (n = 247)
All AEs	98.8%	93.1%
Serious AEs	25.0%	25.9%
AEs leading to		
Interruption	5.0%	10.1%
Discontinuation	13.3%	15.4%
Dose reduction	16.9%	15.8%
Dose delay	35.2%	32.4%
Fatal AEs	4.0%	7.3%
Fatal AEs (treatment-related)	1.0%	0.8%

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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Grade 3 and 4 Adverse Events

	Grade 3		Grade 4	
	Eribulin (n = 503)	TPC (n = 247)	Eribulin (n = 503)	TPC (n = 247)
Hematologic events				
Neutropenia	21.1%	14.2%	24.1%	6.9%
Leukopenia	11.7%	4.9%	2.2%	0.8%
Anemia	1.8%	3.2%	0.2%	0.4%
Febrile neutropenia	3.0%	0.8%	1.2%	0.4%
Non-hematologic events				
Asthenia/fatigue	8.2%	10.1%	0.6%	0
Peripheral neuropathy	7.8%	2.0%	0.4%	0
Nausea	1.2%	2.4%	0	0
Dyspnea	3.6%	2.4%	0	0.4%
Mucosal inflammation	1.4%	2.0%	0	0
Hand-foot syndrome	0.4%	3.6%	0	0

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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Conclusions

- EMBRACE met its primary endpoint of prolonged overall survival.
  - Improvement of median overall survival was 2.5 months (23%) with eribulin versus TPC.
  - Clinically meaningful in heavily pretreated patients
    - Median # of prior chemotherapy regimens (range): 4 (1-7)
- Overall response rate and progression-free survival also favored eribulin.
- Clinical benefits were achieved with a manageable safety profile.
- These results potentially establish eribulin as a new option for women with heavily pre-treated mBC.

Twelves C et al. *Proc ASCO* 2010;Abstract CRA1004.

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Investigator comment on the results of the EMBRACE trial: Eribulin versus treatment of physician's choice

EMBRACE is a nice trial, which took women who were multiply refractory — having received between two and seven prior chemotherapy regimens (median of four) — and randomly assigned them to eribulin versus physician's choice of treatment. At the fourth or fifth line of therapy, there is no right choice and it's difficult to mandate a particular therapy, so this was a great study design. Almost all of the patients had a performance status of 2 or better — in fact, the majority were PS 0 or 1. A major criticism frequently heard is that women receiving late-line therapy will die quickly and have a terrible performance status. That's not true and it's an important take-home message from this trial.

Another important message is that these heavily refractory patients had a statistically significant survival benefit to eribulin of about 20 percent — more than 13 months versus 10.65 months. Importantly, the survival advantage came at little cost in terms of toxicity.

The guidelines state, "Three lines of chemotherapy and that's it." Guess what? With Kim Blackwell's lapatinib/trastuzumab study and EMBRACE, we now have two fourth-line and beyond studies with a survival benefit. So ethically it calls the guidelines into question. I believe the general gestalt amongst community and academic oncologists is that three lines of therapy may not be enough for a lot of women.

Interview with Adam M Brufsky, MD, PhD, June 18, 2010

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Investigator comment on the results of the EMBRACE trial: Eribulin versus treatment of physician's choice

In EMBRACE almost 800 patients who had received between two and five prior regimens for metastatic breast cancer were randomized in a two-to-one ratio to eribulin versus physician's choice monotherapy.

This was a high-risk study design with overall survival as the endpoint, but it was reasonable because patients were not going to be receiving much therapy, if any, thereafter. Eribulin is the first single-agent chemotherapy treatment that has been shown to improve survival in late-line metastatic breast cancer.

Eribulin is a good drug for breast cancer. It's well tolerated and has a good side-effect profile. Not everybody loses their hair. It can cause some neutropenia but febrile neutropenia is fairly low. It doesn't affect hemoglobin or the platelets too much, and the nonhematologic toxicity profile is also quite favorable, in that Grade 3/4 peripheral neuropathy is about eight percent. I've seen great responses with eribulin.

Interview with Linda T Vahdat, MD, June 5, 2010

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