5 Minute JournalClub

POST-SABCS Issue 1, 2013

LEA Trial Evaluating the Addition of Bevacizumab to Endocrine Therapy as First-Line Treatment for Advanced 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

- Apply the results of emerging research evaluating the optimal dose of fulvestrant to the clinical care of postmenopausal patients with locally advanced or metastatic breast cancer.
- Evaluate the contributory effects of bevacizumab when added to standard endocrine therapy for postmenopausal patients with unresectable, locally advanced or metastatic breast cancer.
- Integrate new clinical trial data supporting the extended use of adjuvant tamoxifen beyond 5 years to the treatment of patients with localized estrogen receptor-positive breast cancer.
- Describe the rationale for and emerging efficacy and tolerability data with the novel combination of endocrine therapy and a cyclin-dependent kinase 4/6 inhibitor for postmenopausal women with hormone receptor-positive advanced breast cancer.

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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:

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.

Rowan T Chlebowski, MD, PhD
Professor of Medicine
David Geffen School of Medicine at UCLA
Chief, Division of Medical Oncology and Hematology
Harbor-UCLA Medical Center
Torrance, California

Advisory Committee: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation; Consulting Agreement: Pfizer Inc; Speakers Bureau: Novartis Pharmaceuticals Corporation.

Clifford Hudis, MD
Chief, Breast Cancer Medicine Service
Solid Tumor Division
Department of Medicine
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

No real or apparent conflicts of interest to disclose.

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.

Sir Richard Peto
Professor of Medical Statistics
Co-director, Clinical Trial Service Unit
University of Oxford
Oxford, United Kingdom

No real or apparent conflicts of interest to disclose. Prof Peto was not paid for his interview.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

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This activity is supported by educational grants from Eisai Inc, Genentech BioOncology and Genomic Health Inc.

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: February 2013
Expiration date: February 2014

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POST-SABCS Issue 1, 2013

SABCS highlights: Should adjuvant tamoxifen now be administered for 10 years?

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

In 1995 the National Cancer Institute (NCI) mailed a "Clinical Alert" to oncologists strongly cautioning them to limit the duration of adjuvant tamoxifen (TAM) to 5 years based on data from NSABP and Scottish trials demonstrating no advantage and perhaps a detriment with prolonged endocrine treatment. While investigators worldwide endorsed this recommendation, legendary Oxford statistician Sir Richard Peto and his cadre were not convinced and regularly noted (most memorably in a fiery exchange during the 2000 NIH/NCI Breast Cancer Consensus Conference) that the available data on TAM duration were inadequately powered to answer the question. Further, they believed there was a substantial likelihood that longer treatment would yield greater benefit and to that end championed the launch of 2 massive international trials — ATLAS and **aTTom** — comparing 5 years to 10 years of TAM.

More than a decade later, this past December during the San Antonio Breast Cancer Symposium, Peto (as usual) had the last word when his colleague Richard Gray presented the dramatic findings from the ATLAS trial demonstrating a clear-cut and meaningful advantage in favor of continuing TAM for 10 years. As ATLAS was quite likely the biggest story coming out of the meeting by the river, we decided to kick off this year's post-SABCS series by profiling that and other endocrine-related papers:

1. ATLAS (10 versus 5 years of adjuvant TAM)

Perhaps the most fascinating aspect of this historic study is how ER-positive disease evolves over time and the impressive carryover effect of endocrine treatment that persists for up to a decade after discontinuation. Several weeks after San Antonio, in another in a series of audio interviews I've done with Dr Peto stretching back more than 20 years, he emphasized the profound delayed impact of adjuvant hormonal therapy and pointed out that the full measure of benefit of 10 years of TAM won't be determined until about 2018.

Although more follow-up is welcome, it also seems that there is now a rapidly developing consensus based on the ATLAS findings that treatment should be continued

out to 10 years in patients who remain premenopausal after 5 years of TAM. Treatment for patients who become menopausal during the first 5 years of TAM is far less clear cut, but switching to an aromatase inhibitor and continuing therapy is another logical option. For postmenopausal women with an intact uterus, the risk-benefit profile of 10 years of TAM is controversial.

2. Encouraging data with letrozole in combination with a cyclin-dependent kinase (CDK) inhibitor

CDKs play a critical role in regulating cell-cycle progression, and laboratory evidence suggests possible synergy between CDK inhibition and endocrine treatment. Those observations led to a randomized Phase II trial in postmenopausal women comparing the CDK inhibitor PD 0332991 combined with letrozole to letrozole alone, which at San Antonio demonstrated an improvement in progression-free survival (PFS) from 7.5 to 26.1 months in favor of the combination, with minimal additional toxicity, mainly myelosuppression. Although there was considerable excitement surrounding these impressive results, all agree that a Phase III trial will determine if this is for real or just iniparib-esque hype that will lead to disappointment.

3. Survival benefit of 500 mg vs 250 mg fulvestrant

With an overall survival (OS) hazard rate of 0.81, this is one of the few Phase III breast cancer trials of any type that shows that dose really can matter. The study supports the current widely used practice of administering 500-mg fulvestrant, and one wonders if this fascinating agent will ever be studied in an adjuvant trial.

4. Bevacizumab (bev) and endocrine treatment for metastatic disease (LEA trial)

Same old story here as this Phase III study demonstrated a modest trend for PFS benefit in favor of bev without any effect on survival. This leads to a logical question: Is this the end of the line for anti-angiogenic agents in breast cancer until the ECOG adjuvant bev trial results mature? The answer is not as simple as you might think given the **surprising positive trial results recently reported in metastatic gastric cancer** showing a PFS and OS advantage for monotherapy with a monoclonal antibody to the VEGF receptor 2 (ramucirumab) suggesting that we may not have seen the end of positive research findings with this strategy.

5. SWOG-S1207: Adjuvant everolimus with endocrine treatment

This important study, highlighted during the conference's ongoing clinical trials session, supports the notion that "the best clinical option is often trial participation." Many patients with ER-positive, HER2-negative tumors have less than optimal long-term outcomes with endocrine treatment and chemotherapy, and this study allows patients

the opportunity to maybe fare better by adding an agent with encouraging supportive data in the metastatic setting.

Next in this series: Metastatic HER2-positive disease — where the world awaits the much-needed approval of the antibody-drug conjugate trastuzumab emtansine (T-DM1), and we review more data from San Antonio on the other major recent addition to the field, the HER2 dimerization inhibitor pertuzumab.

Neil Love, MD
Research To Practice
Miami, Florida

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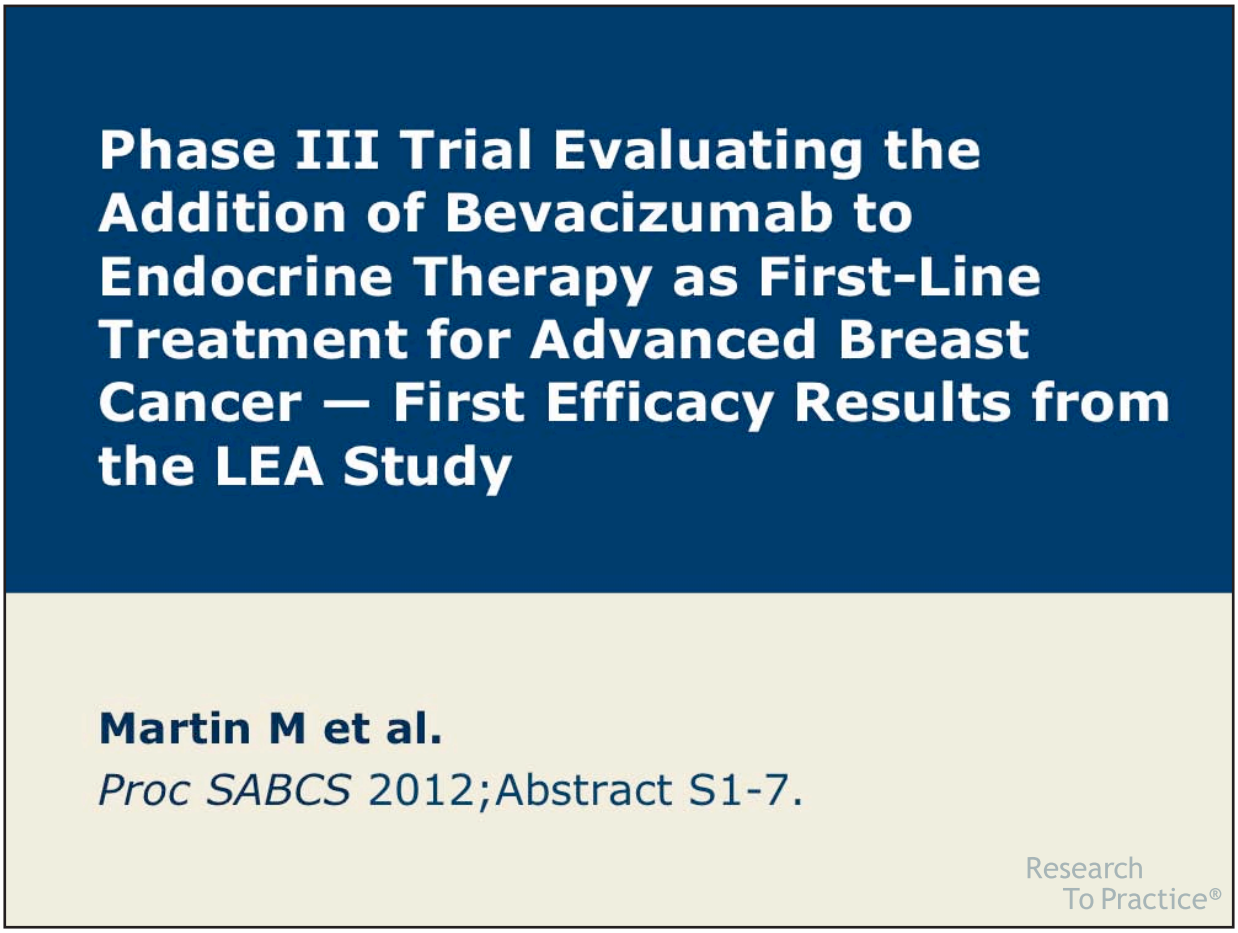
LEA Trial Evaluating the Addition of Bevacizumab to Endocrine Therapy as First-Line Treatment for Advanced Breast Cancer

Presentation discussed in this issue

Martin M et al. **Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer — First efficacy results from the LEA study.** San Antonio Breast Cancer Symposium 2012;**Abstract S1-7**.

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



Background

- High vascular endothelial growth factor (VEGF) levels in tumor tissue from breast cancer are associated with a decreased response to endocrine therapy.
- Downregulation of VEGF may overcome resistance and improve efficacy of hormonal therapy (*JCO* 2005;23:4695-704).
- The combination of endocrine therapy with bevacizumab has been shown to be safe and active in Phase II trials (*JCO* 2010;28:628-33).
- **Objective:**
  - Determine if anti-VEGF treatment can delay resistance to endocrine therapy in patients with hormone receptor-positive advanced breast cancer.

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

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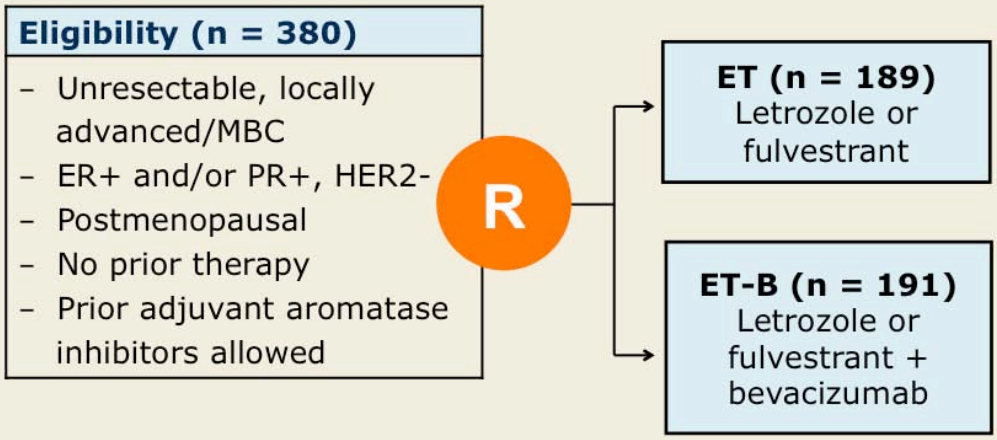
LEA Phase III Study Design



A median progression-free survival (PFS) improvement from 9 months in the ET arm to 13 months in the ET-B arm was assumed (HR = 0.69), requiring a total of 232 PFS events and 354 patients (80% power, 2-sided alpha level of 5%).

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

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Survival Outcomes

	ET (n = 189)	ET-B (n = 191)	HR	*p*-value
Median PFS	13.8 mo	18.4 mo	0.83	0.14
PFS events	131	117*	—	—
Median OS	42 mo	41 mo	1.18	0.469
OS events	42	42	—	—

* Seven while on treatment

OS = overall survival

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

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Select Treatment-Related Adverse Events

Grade 3/4 AEs	ET	ET-B	*p*-value
Anemia	0.6%	1.1%	NS
Leukopenia	0%	2.1%	NS
Fatigue	0.6%	2.1%	0.373
Hypertension	0%	3.2%	0.03
Liver enzyme elevation	0%	1.6%	0.249
Proteinuria	0%	1.1%	0.499
Thromboembolic events	0%	2.1%	0.124

NS = not significant

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

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Author Conclusions

- No statistically significant increase was seen in PFS for ET with bevacizumab versus ET alone.
- An increase of smaller magnitude (ie, <31% reduction in PFS with bevacizumab) cannot be ruled out.
- Adding bevacizumab to ET as first-line therapy had no impact on overall survival.
- Biomarker studies can help to select the population that might benefit from bevacizumab in addition to hormonal treatment.

Martin M et al. *Proc SABCS* 2012;Abstract S1-7.

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Investigator Commentary: Phase III LEA Study on the Addition of Bevacizumab to Endocrine Therapy for Advanced BC

The LEA study demonstrated that the addition of bevacizumab to endocrine therapy resulted in an improvement in PFS that was not statistically significant, and there was no change in overall survival. More toxicity occurred on the arm with bevacizumab, but it was reasonably well tolerated. Our conventional selection criteria are not designed for anti-angiogenic agents, which have nothing to do with the tumor but everything to do with the microenvironment. Unless we come up with a selection strategy for these agents, it is going to be difficult to incorporate them into our armamentarium.

Interview with Lisa A Carey, MD, January 17, 2013

All of the studies to date have consistently shown that adding bevacizumab to therapy improves PFS without having an effect on overall survival. The results of the LEA study are consistent with previous studies. Bevacizumab remains an interesting agent in breast cancer, but it does not change the outcome of the disease enough to warrant its routine use.

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

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