



POST-SABCS Issue 1, 2013

**Final Overall Survival Analysis
of CONFIRM Trial of 500 mg
versus 250 mg of Fulvestrant**

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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:

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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

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

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Final Overall Survival Analysis of CONFIRM Trial of 500 mg versus 250 mg of Fulvestrant

Presentation discussed in this issue

Di Leo A et al. **Final analysis of overall survival for the Phase III CONFIRM trial: Fulvestrant 500 mg versus 250 mg.** San Antonio Breast Cancer Symposium 2012;[Abstract S1-4](#).

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

Final Analysis of Overall Survival for the Phase III CONFIRM Trial: Fulvestrant 500 mg versus 250 mg

Di Leo A et al.

Proc SABCS 2012;Abstract S1-4.

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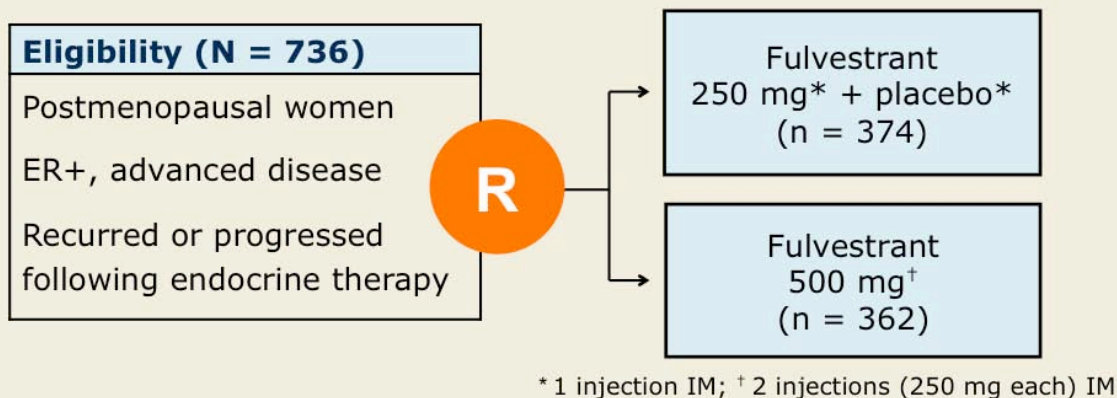
Background

- Primary analysis of the CONFIRM trial for postmenopausal women with locally advanced or metastatic breast cancer demonstrated that with fulvestrant 500 mg versus 250 mg.
 - A statistically significant increase in progression-free survival was recorded (median PFS: 6.5 vs 5.5 months, $p = 0.006$).
 - The median overall survival was 25.1 months and 22.8 months, respectively, after the death of 50% of patients ($p = 0.091$).
(*J Clin Oncol* 2010;28:4594-600)
- **Study Objective:** To present follow-up analysis of overall survival after the death of 75% of patients on the trial.

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

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CONFIRM Study Design



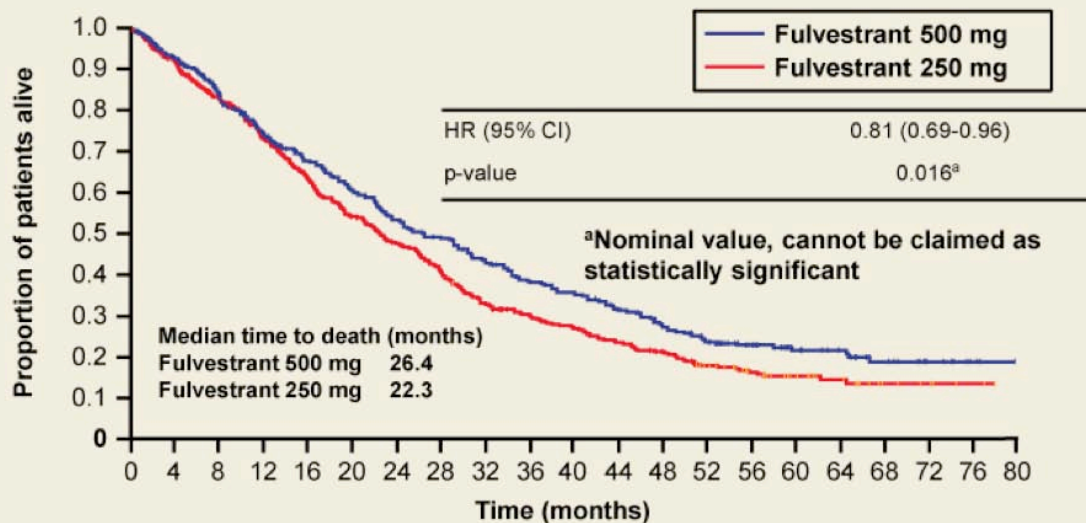
After the primary analysis:

- 50% of patients had died
- Patients on fulvestrant 250 mg were permitted to cross over to 500 mg

Di Leo A et al. *Proc SABCS* 2012;Abstract S1-4.

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Secondary Endpoint: Overall Survival



With permission from Di Leo A et al. *Proc SABCS 2012*;Abstract S1-4.

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First Subsequent Therapies

Type of first subsequent therapy	Fulvestrant 500 mg (n = 230)*	Fulvestrant 250 mg (n = 239)*
Chemotherapy/anti-HER2	59%/0%	59%/0.4%
Endocrine therapy other than fulvestrant [†]	35%	31%
Objective response/clinical benefit	8%/33%	8%/41%

* Patients with available information

[†] 2.1% (8/374) of patients crossed over from 250 mg to 500 mg of fulvestrant.

Di Leo A et al. *Proc SABCS 2012*;Abstract S1-4.

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Select Serious Adverse Events (SAEs) with Outcome of Death

SAEs	Fulvestrant 500 mg (n = 361)	Fulvestrant 250 mg (n = 374)
Acute myocardial infarction	0%	0.5%
Acute renal failure	0%	0.3%
Cardiopulmonary failure	0.3%	0%
Dyspnea	0.6%	0%
Hypertension	0%	0.3%
Meningitis	0%	0.3%

Patients with at least 1 SAE: Fulvestrant 500 mg = 9.7%; fulvestrant 250 mg = 7.2%
Total SAEs: Fulvestrant 500 mg = 1.4%; fulvestrant 250 mg = 1.9%

Di Leo A et al. *Proc SABCS 2012*;Abstract S1-4.

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Author Conclusions

- Final OS analysis at 75% maturity shows that fulvestrant 500 mg is associated with a 4.1-month increase in median OS and a 19% reduction in the risk of death compared to 250 mg of fulvestrant.
- These results are consistent with previously reported PFS and OS data (*J Clin Oncol* 2010;28:4594).
- Analysis of first subsequent therapies does not support any imbalance between the study arms.
- Only 2% of patients crossed over from 250 to 500 mg. However, activity for fulvestrant 500 mg after pretreatment with 250 mg of fulvestrant is unknown.
- The safety results are consistent with those previously reported for 500 mg of fulvestrant.

Di Leo A et al. *Proc SABCS 2012*;Abstract S1-4.

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Investigator Commentary: Final Analysis of the Phase III CONFIRM Trial: Fulvestrant 500 mg versus 250 mg

The CONFIRM trial compared fulvestrant at what used to be the conventional dose of 250 mg versus 500 mg in postmenopausal women with advanced breast cancer. The first analysis demonstrated an improvement in progression-free survival and a nonsignificant increase in overall survival.

This study was the final analysis of overall survival after 75% of the events had occurred. One cannot argue with the improvement in overall survival. The results showed a 4-month improvement in overall survival and a 19% reduction in the risk of death.

Only 2% of the patients crossed over from the 250-mg to the 500-mg dose. An analysis of the first subsequent therapy showed that both the arms were similar and most of the patients went on to receive chemotherapy. It is unlikely that imbalance between the 2 arms altered the survival results. Based on the results of this study, I would administer fulvestrant at 500 mg in my practice.

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

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