5 Minute JournalClub

POST-SABCS Issue 1, 2013

ATLAS Trial of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years for Early 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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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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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.

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ATLAS Trial of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years for Early Breast Cancer

Presentation discussed in this issue

Davies C et al. **Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.** *Lancet* 2012;[Epub ahead of print]. **Abstract**

Slides from a presentation at SABCS 2012 and transcribed comments from recent interviews with Sir Richard Peto (1/11/13) and Rowan T Chlebowski, MD, PhD (1/9/13)

Background

- For women with estrogen receptor (ER)-positive early breast cancer, previous studies have shown that treatment with tamoxifen (TAM) for 5 years:
  - Significantly decreases breast cancer recurrence throughout the first 10 years.
  - Substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis (*Lancet* 2011;378:771-84).
- However, little is known about how 10 years of TAM compares to the current standard of treatment for 5 years.
- The randomized Phase III ATLAS trial assessed the effects of continuing TAM therapy for 10 years rather than stopping at 5 years.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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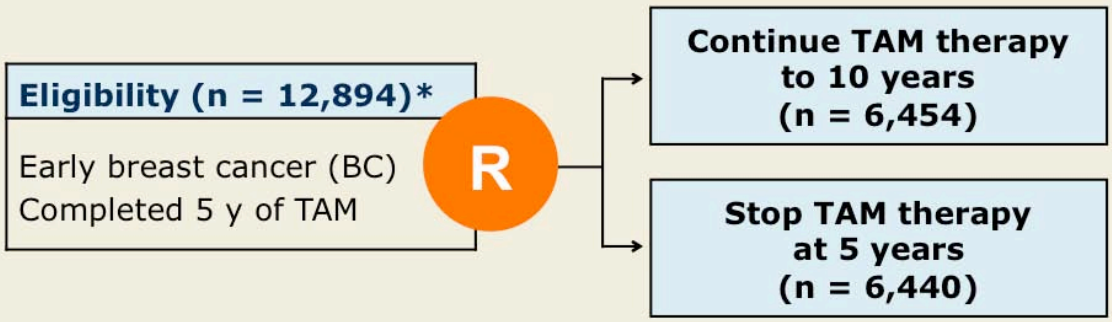
ATLAS Trial Design



* Of the study's entire population, ER-positive BC: 6,846 (53%); ER-negative BC: 1,248 (10%); unknown ER status: 4,800 (37%)

- Yearly follow-up forms sent by central organizers recorded recurrence, incidence of second cancer, hospital admission or death.
- Besides duration of TAM therapy, disease management was at physician's discretion.
- Recurrence was defined as first recurrence of any form of BC after ATLAS entry.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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Recurrence Rate for Patients with ER-Positive BC

No. of years since diagnosis	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
5 y (study entry)	—	—
10 y (treatment end)	13.1%	14.5%
15 y (10 y since study entry)	21.4%	25.1%

- BC recurrences (continuing TAM to 10 y vs stopping at 5 y): 617 vs 711 (2*p* = 0.002)

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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BC Mortality (Overall Rate per Rate in Women without Recurrence) for Patients with ER-Positive BC

No. of years since diagnosis	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
5 y (study entry)	—	—
10 y (treatment end)	5.8%	6.0%
15 y (10 y since study entry)	12.2%	15.0%

- BC mortality (continuing TAM to 10 y vs stopping at 5 y): 331 vs 397 (2*p* = 0.01)

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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Select Adverse Events (Any ER Status)

Event	Continue TAM to 10 y (no.)	Stop TAM at 5 y (no.)	Event RR (2*p*-value)
Second cancer incidence			
Contralateral BC	419	467	0.88 (0.05)
Endometrial cancer*	116	63	1.74 (0.0002)
Nonneoplastic disease†			
Stroke	130	119	1.06 (0.63)
Pulmonary embolus	41	21	1.87 (0.01)
Ischemic heart disease	127	63	0.76 (0.02)

* Mainly endometrial adenocarcinoma but includes all other uterine tumors except cervical cancer; uterine tumors exclude those with recorded hysterectomy at study entry

† Ever hospitalized or died

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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Event Rate Ratios in ER-Positive Disease from Time of Diagnosis in Meta-Analysis and ATLAS Trial

	5 y TAM vs none: Meta-analysis	10 y TAM vs 5 y: ATLAS	10 y TAM vs none*
Breast cancer recurrence ≥10 y	0.94	0.75	0.70
Breast cancer mortality ≥10 y	0.73	0.71	0.52

* Product of rate ratios, estimated effect

"Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10-14 after diagnosis."

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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Side Effects and Main Effects of 10 Years of TAM on 15-Year Mortality in Meta-analysis and ATLAS Trial

	5 y TAM vs none: Meta-analysis	10 y TAM vs 5 y: ATLAS	10 y TAM vs none (by addition)
Endometrial cancer and PE mortality	0.2% loss	0.25 loss	0.4% loss
Breast cancer mortality	9% gain	3% gain	12% gain

Estimated effects of 10 y TAM vs 0 on 15-y mortality:
Absolute gain ~30 x absolute loss

Davies C et al. *Proc SABCS* 2012;Abstract S1-2.

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Author Conclusions

- For women with ER-positive breast cancer, the continuation of TAM treatment for 10 years instead of stopping at 5 years results in a further reduction in recurrence and mortality, especially after year 10.
- The ATLAS study, taken together with results from previous trials of 5 years of TAM treatment versus none, suggests that 10 years of TAM treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

Davies C et al. *Lancet* 2012;[Epub ahead of print].

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Editorial: Extended Adjuvant Tamoxifen for Breast Cancer — A New Era

"Overall the benefits of extended tamoxifen seemed to outweigh the risks substantially. This finding raises questions about the possible benefit of extension of adjuvant endocrine therapy… No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment."

"Confirmation of the ATLAS trial by meta-analysis of all extended tamoxifen treatment trials should herald a change of practice, with the standard of care revised to 10 years rather than 5 years of tamoxifen in patients for whom tamoxifen is indicated. This change should open up a whole new era of clinical trials to assess the benefit of extended adjuvant endocrine therapy of breast cancer."

Powles TJ et al. *Lancet* 2012;[Epub ahead of print].

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Investigator Commentary: ATLAS — Long-Term Effects of Continuing Adjuvant TAM for 10 y versus 5 y After Diagnosis

For the ATLAS trial, we wanted results that would apply, globally, to all women with ER-positive BC. Many physicians were uncertain as to whether to continue with TAM beyond 5 y, especially with the alert that going beyond 5 y could be dangerous. We encouraged TAM continuation beyond 5 y when both the patient and physician were substantially uncertain about how to proceed. Although many did not know whether it would be harmful or beneficial, they thought the difference would be minimal either way. ATLAS showed that 10 y is somewhat more effective than 5 y. Even though TAM can cause pulmonary embolus and endometrial cancer, the gain albeit small, is 10 times more than the hazards in terms of life or death. ATLAS should be seen as a trial of longer versus shorter hormonal endocrine therapy (ET). The conclusion that 10 y is a little better than 5 y of ET points to the prevention of cancer recurrence and improved long-term survival. I believe that this conclusion will continue to hold even if treatment moves on from TAM to other such agents.

Interview with Sir Richard Peto, January 11, 2013

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Investigator Commentary: ATLAS — Long-Term Effects of Continuing Adjuvant TAM for 10 y versus 5 y After Diagnosis

Sir Richard Peto will certainly tell you he believed the existing data were not definitive, so he wanted to do a study. ATLAS was a controversial trial, but Professor Peto felt that the biology was in favor of longer TAM duration. It is remarkable that they were able to get the study under way. It is a practice-changing trial that gets us thinking about the nature of BC and ET.

The results are fascinating, demonstrating that after 5 y of TAM, continuing versus stopping TAM produces little effect in year-5 to year-10 while administering treatment (hazard ratio of 0.9). Thereafter, in year 10 to year 15 the authors reported statistically significant reductions in BC incidence, BC mortality and overall mortality for women with ER-positive disease. These results are spectacular.

Interview with Rowan T Chlebowski, MD, PhD, January 9, 2013

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