



POST-SABCS Issue 5, 2013

PHARE: 6 Months versus 12 Months of Adjuvant Trastuzumab

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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

- Determine the optimal duration of trastuzumab administration in the adjuvant setting using recent clinical trial evidence evaluating 1 year of adjuvant trastuzumab versus 6 months or 2 years.
- Assess the long-term survival outcomes of patients receiving 1 year of adjuvant trastuzumab combined with chemotherapy in comparison to those receiving only chemotherapy, and consider this information in the management of early HER2-positive breast cancer.
- Evaluate the association between immune biomarkers and clinical responses to trastuzumab and pertuzumab as support for the potential use of combined HER2-targeted and immunomodulatory agents.

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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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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,
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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, Bodesix 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: May 2013

Expiration date: May 2014

Key Papers on Adjuvant and Neoadjuvant Treatment of HER2-Positive Breast Cancer

To go directly to slides and commentary for this issue, [click here](#).

It's now coming up on 8 years since that warm May day in Orlando when Dr George Sledge chaired the historic ASCO session during which the very first Phase III data sets confirming the benefit of adjuvant trastuzumab (T) with chemotherapy were unveiled. In San Antonio this past December we witnessed perhaps the final meaningful remnants of that generation of landmark studies while also getting a peek at the next set of relevant issues currently being addressed in ongoing trials. So to close out this year's SABCS highlights series we look at several of the most intriguing presentations focused on the management of early HER2-positive disease.

1. Duration of adjuvant trastuzumab: **HERA** and **PHARE** trials

During a CME symposium our group hosted on the first night of the conference, the ever-mirthful Dr Sledge was tasked with reviewing this pragmatic topic, and to get things started the first slide he showed was a beautiful photo of the earth orbiting the sun. Of course, Dr Sledge's visual metaphor related to the conclusion that he and most investigators had come to accept following the presentations of the HERA and PHARE data sets last October at the 2012 European Society for Medical Oncology Congress in Vienna — that 1 year of adjuvant T remains the optimal duration.

Both of these studies were updated in San Antonio. HERA, presented by Dr Martine Piccart-Gebhart, provided a definitive answer that 2 years of T is not better than 1. On the other hand, the French PHARE trial attempted to build on the signal observed in the underpowered but encouraging FinHer study of 9 weeks of T and compared 6 months to 12 months. During the presentation at San Antonio I got lost in terms like "failed to prove lack of inferiority," but just looking at the numbers, 6 months didn't look quite as efficacious as 12, and the collective sentiment appears to be that we've done the right thing all along by following Dr Sledge's orbital concept.

2. Long-term impact of adjuvant trastuzumab

In a brilliant and detailed analysis presented to the FDA in early 2005, the late NSABP statistician Dr John Bryant proposed that combining the data from 2 ongoing simultaneous adjuvant T trials (NSABP-B-31 and NCCTG-N9831) not only was feasible but also would help to obtain a quicker answer for patients, particularly as clinicians in practice grew increasingly uncomfortable holding the line at not using this relatively nontoxic agent with such a great likelihood of success. The FDA agreed with this premise, and later that year I had the pleasure of interviewing the NSABP's Dr Edward Romond just moments after his presentation to the ASCO multitudes of this combined data set. During this memorable conversation Dr Romond's voice was tremulous with emotion as he recounted for our audio audience the amazing history leading to that moment.

Dr Romond was again center stage in San Antonio, presenting the 10-year survival data from that landmark combined effort. The data reveal that the effects of treatment were similar regardless of ER status (this was also seen in HERA) and the survival benefit was still maintained although somewhat attenuated due to crossover to T once the data were released (20% crossover in the NSABP/NCCTG data and an unprecedented 52% in HERA). However, the profound impact of this advance can be understood from a different perspective when we consider the final numbers from this analysis of 4,046 patients: 391 vs 227 patients with distant recurrence; 381 vs 234 deaths from breast cancer; 206 vs 137 deaths among patients with ER and/or PR-positive tumors; 212 vs 149 deaths among patients with ER and PR-negative tumors.

3. The way forward? Initial evidence suggesting a potential future role for immune checkpoint inhibitors combined with anti-HER2 agents

As this first adjuvant HER2 chapter closes, others on the horizon will soon open, and when one asks investigators which current study or concept seems most promising, the first response is quite frequently the classically straightforward but immensely interesting APHINITY trial comparing adjuvant chemotherapy/T with or without the HER2 dimerization inhibitor pertuzumab. The enthusiasm for this compelling concept is partially related to prior data from the Phase II NeoSphere trial presented by Dr Luca Gianni, which demonstrated a marked increase in pathologic CRs when pertuzumab was added to chemotherapy/T in the neoadjuvant setting.

As in many contemporary neoadjuvant trials, a critical component of NeoSphere was the collection and analysis of tumor tissue, and at San Antonio Dr Gianni presented thought-provoking findings that expression of immune-based biomarkers, including PD-1, PD-L1, CTLA-4 and others, may predict benefit from HER2-directed therapies. These hypothesis-generating data may open the door to a new frontier in which anti-HER2 therapy is combined with the immune modulators that are offering so much hope

in melanoma, renal cell carcinoma, lung cancer and other challenging neoplasms. It will be fascinating to compare the NeoSphere translational findings to those about to be presented with the very first oral breast cancer paper at the upcoming ASCO meeting by Dr Lisa Carey from a major CALGB neoadjuvant HER2 study that also includes extensive tissue correlates.

This concludes our annual San Antonio wrap-up. Keep an eye out for our upcoming pre-ASCO email/video program with highlights from a recent breast cancer clinical investigator Think Tank with more on these and other new data sets and trial concepts.

Neil Love, MD

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PHARE: 6 Months versus 12 Months of Adjuvant Trastuzumab

Presentation discussed in this issue

Pivot X et al. **PHARE trial results of subset analysis comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer.** San Antonio Breast Cancer Symposium 2012; **Abstract S5-3**.

Slides from a presentation at SABCS 2012 and transcribed comments from a recent presentation by George W Sledge Jr, MD (12/5/12)

PHARE Trial Results of Subset Analysis Comparing 6 to 12 Months of Trastuzumab in Adjuvant Early Breast Cancer

Pivot X et al.

Proc SABCS 2012;Abstract S5-3.

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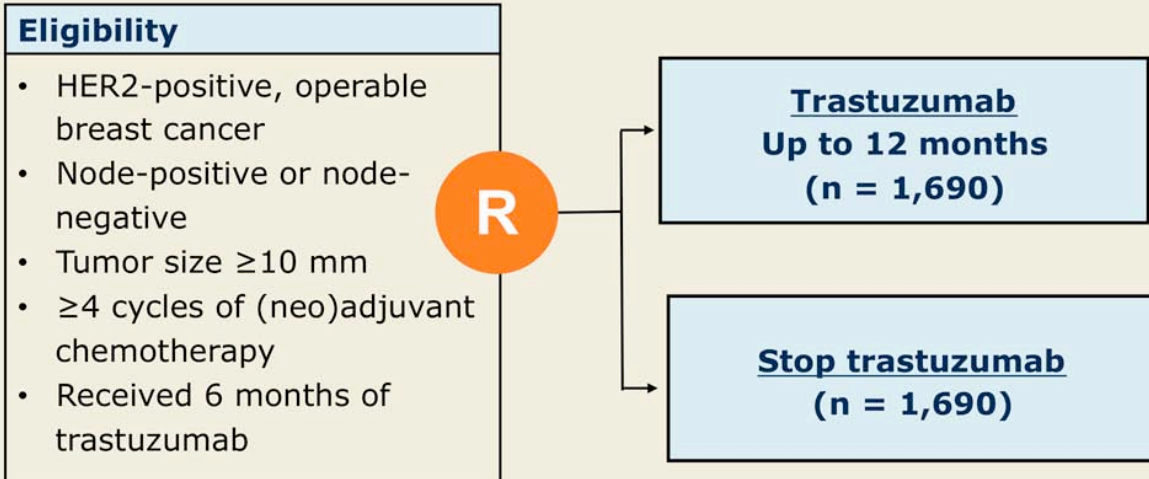
Background

- Since 2005, 4 large Phase III studies have demonstrated improvement in overall survival with the addition of 1 year of trastuzumab to adjuvant chemotherapy for patients with HER2-positive early breast cancer (*NEJM* 2005;353(16):1673; *NEJM* 2005;353(16):1659; *Proc SABCS* 2006;Abstract 52).
- The FinHER study showed that 9 weeks of adjuvant trastuzumab was safe and effective for HER2-positive early breast cancer (*JCO* 2009;27(34):5685).
- The optimal duration of adjuvant trastuzumab remains uncertain, and concerns about cardiac toxicity persist.
- **Current study objective:** To evaluate 6 months and 12 months of adjuvant trastuzumab for patients with early breast cancer.

Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

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PHARE Noninferiority Trial Design



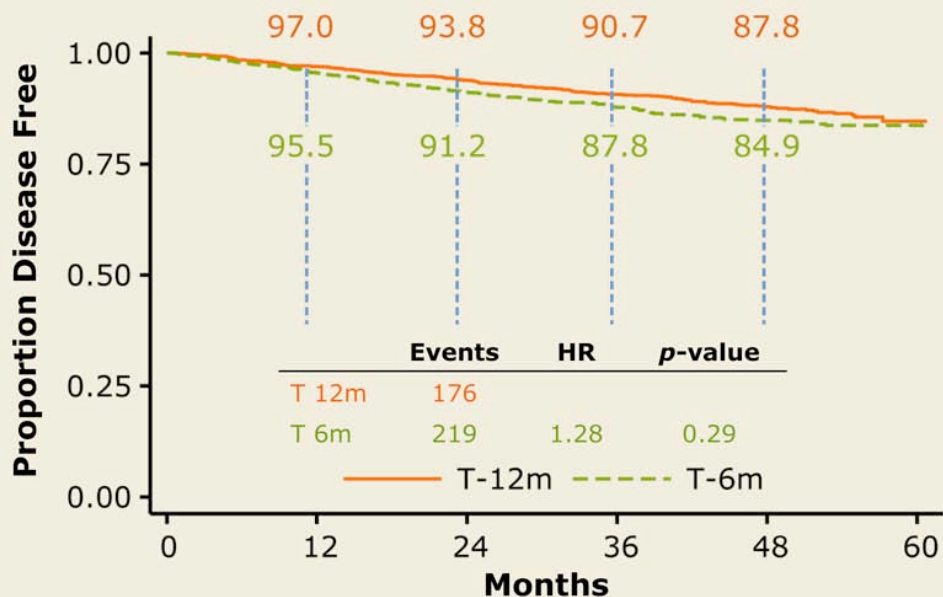
Primary endpoint: Disease-free survival

Noninferiority design: 2% variation in absolute difference in recurrence; 95% CI HR margins should not cross the 1.15 boundary

Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

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Disease-Free Survival

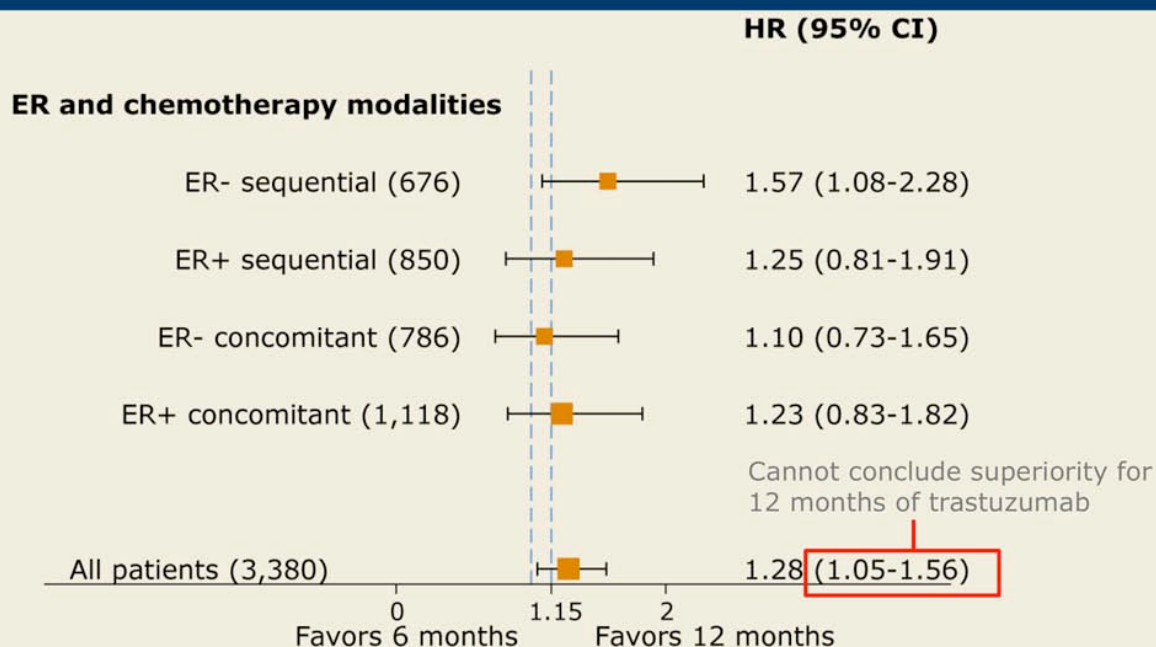


Stratified by ER status and concomitant chemotherapy

With permission from Pivot X et al. *Proc SABCS 2012*; Abstract S5-3.

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Disease-Free Survival: Sub-Group Analysis



With permission from Pivot X et al. *Proc SABCS 2012*; Abstract S5-3.

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Author Conclusions

- PHARE failed to show that 6 months of trastuzumab is noninferior to 12 months.
- Subgroup analyses suggested:
 - Sequential modality for ER-negative tumors affected the overall results.
 - Results in other groups seemed compatible with the noninferiority hypothesis.
- PHARE longer follow-up and PERSEPHONE, SHORT-HER and SOLD trial results are expected.

Pivot X et al. *Proc SABCS 2012*;Abstract S5-3.

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Investigator Commentary: Six versus 12 Months of Adjuvant Trastuzumab in the PHARE Study

Several trials have evaluated the duration of adjuvant trastuzumab. Two of these studies — PHARE and HERA — were recently updated at the 2012 San Antonio Breast Cancer Symposium. Collectively, these studies involve more than 8,000 patients, and another 5,000+ patients will subsequently be analyzed in other trials.

What are these trials showing us? HERA compared 2 years to 1 year of adjuvant trastuzumab. Clearly no difference exists, so we have absolutely no reason to believe that continuing adjuvant trastuzumab past a year would benefit our patients.

How about 6 months versus 1 year? With about 4 years of follow-up, the PHARE study shows an approximately 2.9% absolute difference in disease-free survival favoring 1 year versus 6 months of adjuvant trastuzumab. This is not a statistically significant difference. Importantly, this was a noninferiority rather than a superiority trial, and the 95% confidence interval HR margins should not cross the 1.15 boundary. Strictly speaking, this study does not demonstrate the superiority of 1 year over 6 months of adjuvant trastuzumab. At least to date, 1 year of adjuvant trastuzumab appears to be scientifically supported, but of course we'll have other follow-up data that will emerge in the next few years.

Presentation by George W Sledge Jr, MD, December 5, 2012