



POST-SABCS Issue 5, 2013

Association between the Adaptive Immune System and Immune Checkpoints and Response to Pertuzumab and 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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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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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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Miami, Florida

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Association between the Adaptive Immune System and Immune Checkpoints and Response to Pertuzumab and Trastuzumab

Presentation discussed in this issue

Gianni L et al. **Adaptive immune system and immune checkpoints are associated with response to pertuzumab (P) and trastuzumab (H) in the NeoSphere study.** San Antonio Breast Cancer Symposium 2012;[Abstract S6-7](#).

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

Adaptive Immune System and Immune Checkpoints Are Associated with Response to Pertuzumab (P) and Trastuzumab (H) in the NeoSphere Study

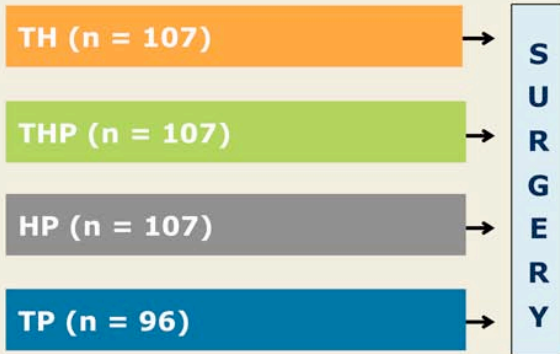
Gianni L et al.

Proc SABCS 2012;Abstract GS6-7.

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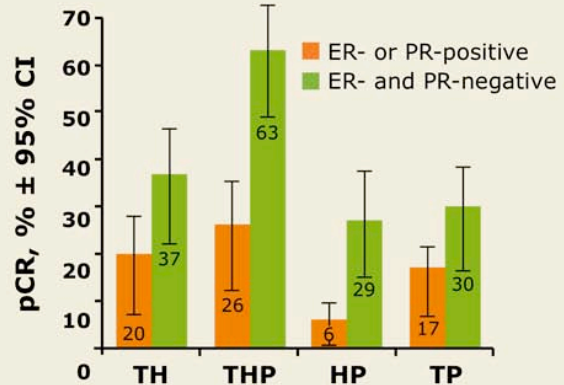
Background

NEOSPHERE Phase II study in HER2-positive operable, locally advanced or inflammatory breast cancer (N = 417)



T = docetaxel (75 → 100 mg/m²)
H = trastuzumab (8 → 6 mg/kg)
P = pertuzumab (840 → 420 mg)

Study dosing: q3wk x 4



- Trastuzumab and pertuzumab work by inhibiting HER receptor activation and by cytotoxic immune mechanisms.
- This study assessed the association of preselected immune biomarkers with pathologic complete response (pCR).

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Methods

- Tumor samples collected in 98% of patients in NEOSPHERE:
 - mRNA extracted from 93% of patients
 - Gene expression profiles from 88% of patients
- Association of pCR in breast or residual disease with
 - Age, clinical nodal status, clinical stage, ER/PR status, treatment
 - Selected immune biomarkers (genes and metagenes expression) based on expected biologic relevance

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Selection of Immune Biomarkers Based on Expected Biologic Relevance

Metagenes*

Specific immune cell subtypes

- **CD8A (CD8/~NK)**
- **IGG (immunoglobulins)**
- **MHC2 (dendritic cells)**

Genes under control of common transcription factors

- **STAT1** (GBP1, STAT1, CXCL10, CXCL11)
- **Interferon inducible** (ie, OAS1, IFI44L, MX1, IFIT1, IFIT2)
- **MHC1** (HLA Class I, ie, G, F, A, E)

Individual Genes

- **IFNY**

Key immune regulatory gene, also modulating PD-L1 expression by tumor cells

Genes associated with immune checkpoints **and target of therapies**

- PD-L1
- PD-L2
- PD-1
- CTLA4

* **Metagenes:** Average expression of highly correlated genes describing similar functions or under control of the same transcription factors

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Association of Select Gene Expression Patterns/Clinical Variables with pCR and Residual Disease

- Multivariate analysis demonstrated common immune biomarker patterns with pertuzumab in the HP and TP treatment arms:
 - High PD-1 expression was associated with high pCR.
- Analysis of the trastuzumab-containing arms, TH and HP, showed that
 - High expression levels of interferon-inducible gene (IF-I) were associated with residual disease.
 - High expression levels of dendritic cell metagene (MHC2) were associated with high pCR.
- Analysis of 3 arms (TH, HP and TP) demonstrated that
 - High PD-L1 expression was associated with residual disease.
 - High STAT1 expression was associated with pCR.
- Young age and ER-negative status were associated with pCR.

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Multivariate Analysis of Immune-Related Gene Expressions with THP Therapy

- A significant interaction was observed between ER status and the following genes:
 - Interferon-gamma (IFN-gamma) ($p = 0.0003$)
 - PD-L1 ($p = 0.025$)
 - CTLA4 ($p = 0.009$)
- In ER-negative tumors
 - High gene expression levels of PD-L1 ($p = 0.016$) and CTLA4 ($p = 0.007$) were associated with residual disease.
 - High expression levels of IFN-gamma were associated with high pCR ($p = 0.002$).
- In contrast, in ER-positive tumors high expression of the IFN-gamma gene was associated with residual disease ($p = 0.018$).
- Overall, there was a clear indication that T-cell activation was associated with pCR.

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Author Conclusions

- Adaptive immune mechanisms seem to modulate benefit from HER2-directed therapies.
- High PD-L1 expression was strongly associated with residual disease consistently in all arms and with all treatments.
- In a treatment-dependent and ER status-dependent way,
 - High pCR was associated with high expression of 1 or more among IFN γ , STAT1, MHC2, CD8A and/or PD-1.
 - Probability of residual disease was associated with high expression of CTLA4, MHC1 and interferon-inducible genes.

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Author Conclusions (Continued)

- Confirmation of the involvement of adaptive immune mechanisms in the therapeutic effects of the HER2-directed therapies is ongoing in different case trials and with different assays.
- Available findings
 - Provide a rationale for combining HER2-targeted treatments with immune-modulating agents
 - May allow for the prediction of treatment benefit

Gianni L et al. *Proc SABCS 2012*;Abstract GS6-07.

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Investigator Commentary: Adaptive Immune System and Immune Checkpoints and Response to Pertuzumab and Trastuzumab

The NEOSPHERE trial addressed the dual HER2-targeting issue in the neoadjuvant setting. Patients with HER2-positive breast cancer all received neoadjuvant trastuzumab with or without pertuzumab, with or without docetaxel. The focus in this particular analysis was targeting the immune checkpoints.

Investigators evaluated a number of the immune-related genes, including PD-1, PD-L1 and others. A circle of activity that was observed has been described as the adaptive immune resistance mechanism of these cancer cells, producing factors that are inhibitory to the immune system. Some therapeutically relevant players were evaluated. The relationship of each of these immune-related genes and checkpoint genes to pCR was examined. The intriguing aspect of this study is that some of these biomarkers may be therapeutically targetable. I believe this may be the next frontier. These data add to the supposition that a therapeutic rationale might exist for combining cytotoxic drugs with anti-HER2 agents because ADCC induction is one mechanism of action for these monoclonal antibodies.

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