5 Minute JournalClub

Key SABCS Presentations

Issue 1, 2011

Combination of Trastuzumab, Pertuzumab and Docetaxel as Neoadjuvant Therapy in the Management of Previously Untreated HER2-Positive Early, Locally Advanced and Inflammatory Breast Cancer

For more visit ResearchToPractice.com/5MJCSABCS2011

Research To Practice®

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. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. 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 meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVES

- Recall new data to support the adjuvant investigation of pertuzumab in combination with trastuzumab without chemotherapy in HER2-positive early breast cancer.
- Describe the efficacy and safety of the neoadjuvant docetaxel/trastuzumab/pertuzumab combination for patients with HER2-positive early, locally advanced or inflammatory breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Luca Gianni, MD
Director of Medical Oncology 1
Department of Medical Oncology
Istituto Nazionale Tumori di Milano
Milan, Italy

Advisory Committee: Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Eisai Inc, Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis; Consulting Agreements: Biogen Idec, GlaxoSmithKline, Millennium Pharmaceuticals Inc.

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: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/ Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium Pharmaceuticals Inc, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Last review date: January 2011
Expiration date: January 2012

5 MinuteJournalClub

Key SABCS Presentations
Issue 1, 2011

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

Sometimes the cavernous San Antonio conference hall can be so devoid of attendees that you feel like you could throw a Frisbee® and not hit anyone. But on Friday, December 10, 2010 at 9 AM, even the spillover video simulcast section was standing room only. The occasion was the presentation of three highly anticipated neoadjuvant trials for patients with HER2-positive tumors. To begin this memorable session, Duke's Neil Spector gave a superb review of anti-HER2 treatment, which he ended with a photo of himself wired up in a hospital gown taken shortly after a heart transplant. (He implored the audience to sign their organ donor cards.) Eric Winer finished things off with an enlightening and thought-provoking follow-up discussion that he told me had him up until 3 AM the night before changing slides. In between, there was plenty to warrant the massive crowd.

To start off this series of eight weekly reports from San Antonio, here's the bottom line on these historic neoadjuvant HER2 data sets.

1. **German GeparQuinto study: More path CRs with trastuzumab/chemo than lapatinib/chemo**
In the first reported head-to-head comparison of these two commonly used anti-HER2 agents, Michael Untch demonstrated that the antibody won out over the TKI with a pCR rate (in breast and nodes) of 31.3 percent versus 21.7 percent. A second study reported at SABCS (see below) also showed an advantage to trastuzumab over lapatinib but was not considered statistically significant. Although it may not matter in the long run, much debate has focused on whether this interesting finding is related to an inherent difference in the antitumor efficacy of these agents or the fact that some patients randomly assigned to lapatinib ended up receiving less drug as a result of discontinuation of therapy due to toxicity.

2. **Neo-ALTTO trial: More pCRs with chemo/trastuzumab/lapatinib than with chemo plus either anti-HER2 agent alone**
In a parallel trial design to the ongoing 8,000-plus-patient international adjuvant trial, this much-awaited neoadjuvant study evaluated chemo with trastuzumab, lapatinib or the combination, and as reported by José Baselga, the dual anti-HER2 arm doubled the pCR rate to 46.9 percent. Although few, if any, investigators are suggesting this approach outside a protocol setting, perhaps this is a first glimpse at where we'll end up in the next few years.

3. **NEOSPHERE study: Chemo/trastuzumab versus chemo/pertuzumab versus chemo/trastuzumab/pertuzumab versus trastuzumab/pertuzumab**
Luca Gianni (protégé of the legendary Gianni Bonadonna) surprised the multitudes with this study that demonstrated the best pCR rate (39.3 percent) when both antibodies were combined with chemo. However, he also reported an 11.2 percent pCR rate when pertuzumab and trastuzumab were used together without chemo. Pertuzumab — a yet-unavailable agent that inhibits HER2 dimerization — is about to be studied in the adjuvant setting, adding even more hope and potential for the future.

Of course, it will be some time before we know how these neoadjuvant strategies pan out in the long term, but in another important and encouraging paper by the Germans (**the TECHNO trial**), pCR after neoadjuvant trastuzumab/chemo was highly correlated with longer-term disease-free and overall survival. If that finding holds true, then SABCS 2010 will forever be remembered as a harbinger of what is to come in the management of HER2-positive disease.

Next up in this series: The big disappointment of San Antonio — the AZURE trial demonstrates no adjuvant benefit with zoledronic acid.

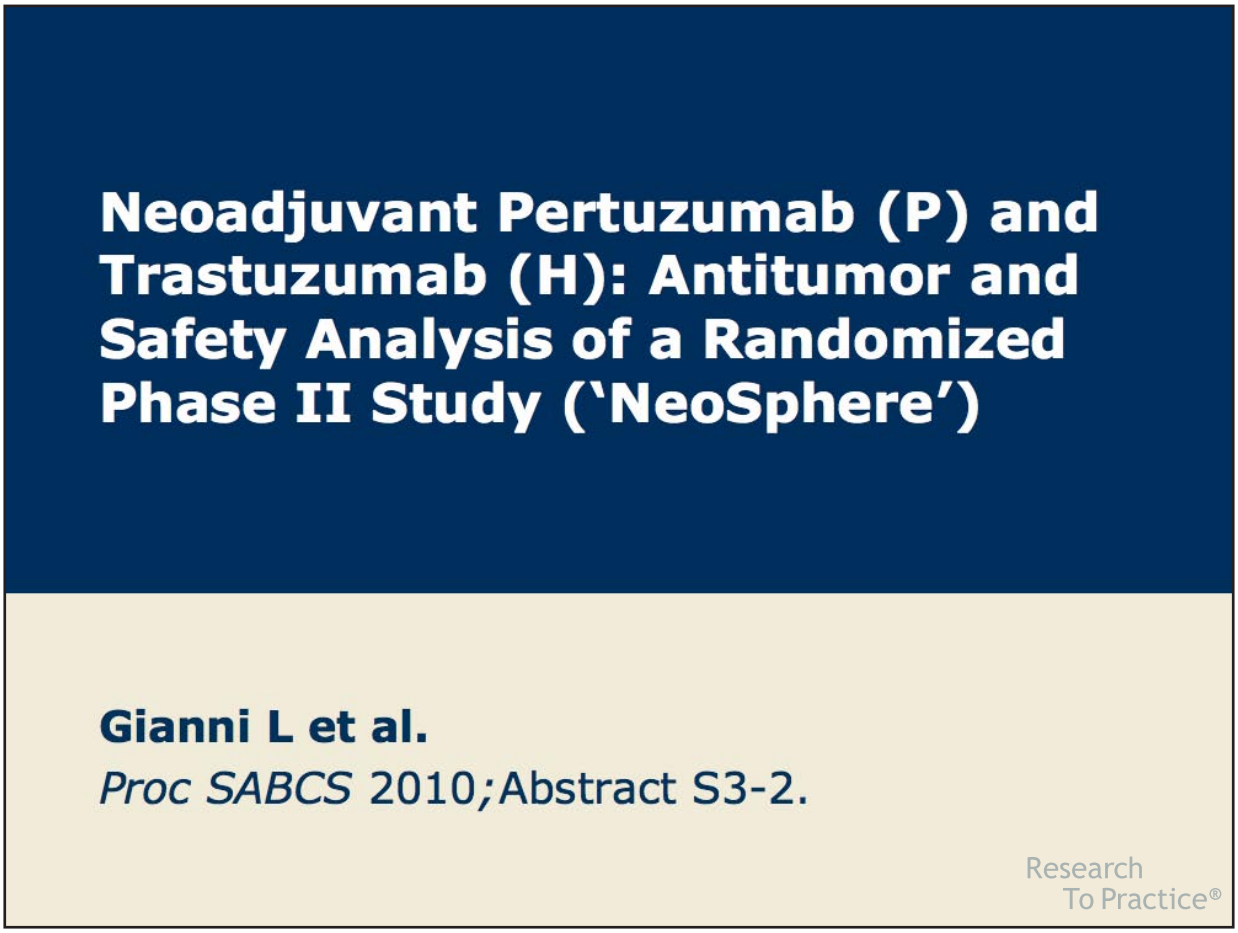
Neil Love, MD
Research To Practice
Miami, Florida

Combination of Trastuzumab, Pertuzumab and Docetaxel as Neoadjuvant Therapy in the Management of Previously Untreated HER2-Positive Early, Locally Advanced and Inflammatory Breast Cancer

Presentation discussed in this issue

Gianni L et al. **Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized phase II study ('NeoSphere').** San Antonio Breast Cancer Symposium 2010;**Abstract S3-2**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Luca Gianni, MD (12/10/10)



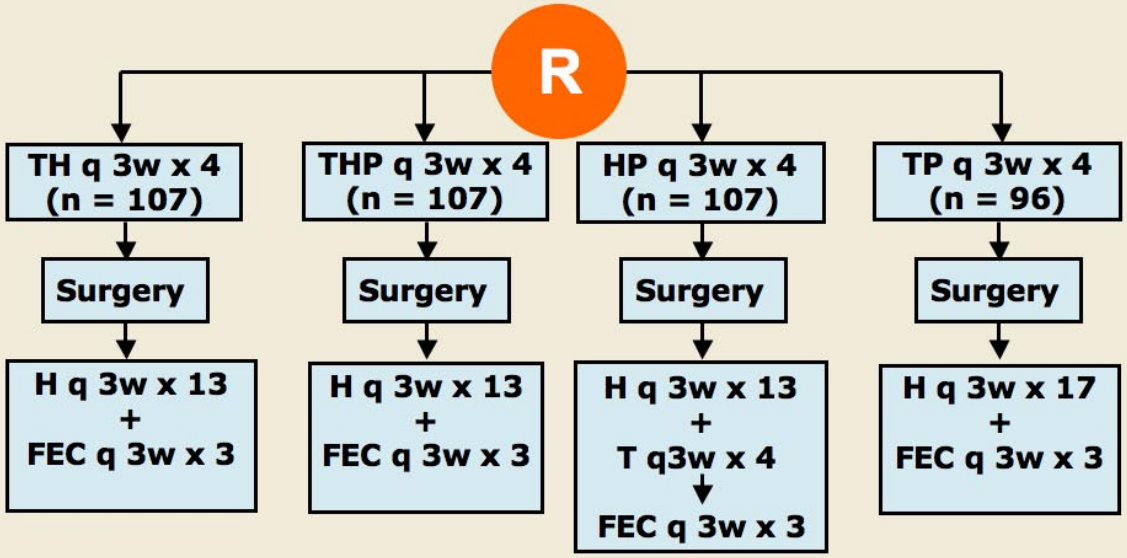
Study Eligibility and Objectives

- Eligibility:
  - Operable or locally advanced/inflammatory breast cancer
  - Centrally confirmed HER2-positive (IHC 3+ or FISH positive)
  - Chemotherapy naïve
  - Primary breast tumor >2 cm
  - No metastasis
- Objectives:
  - Primary: pathological CR (pCR) rates
  - Secondary: clinical response, disease-free survival, breast conservation rate, biomarker evaluation

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Research To Practice®

Study Schema



T = Docetaxel, H = Trastuzumab, P = Pertuzumab
F = 5-fluorouracil, E = Epirubicin, C = Cyclophosphamide

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Research To Practice®

Efficacy Results by Breast and Lymph Nodal Status

	TH (n = 107)	THP (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node positive at surgery	7.5%	6.5%	5.6%	6.3%

The differences between the THP arm and other arms for pCR were statistically significant, with all the *p*-values being <0.05.

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Research To Practice®

Efficacy Results by ER/PR Status

	TH	THP	HP	TP
pCR (ER- or PR-positive)	22.0%	26.0%	5.9%	17.4%
pCR (ER- and PR-negative)	36.8%	63.2%	29.1%	30.0%

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Research To Practice®

Safety Results

	TH (n = 107)	THP (n = 107)	HP (n = 108)	TP (n = 94)
Grade 3-4 neutropenia	57.0%	44.9%	0.9%	55.3%
Febrile neutropenia	7.5%	8.4%	0.0%	7.4%
Grade 3-4 diarrhea	3.7%	5.6%	0.0%	4.3%
Grade 3-4 rash	1.9%	1.9%	0.0%	1.1%
Grade 3-4 increased ALT	2.8%	0.0%	0.0%	1.1%
Serious adverse events	16.8%	10.3%	3.7%	17.0%

Any changes in left ventricular ejection fraction did not appear clinically meaningful and were similar among all the four arms.

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Research To Practice®

Conclusions

- Combination of docetaxel, trastuzumab and pertuzumab (THP) achieved a significantly higher pCR rate when compared to docetaxel-trastuzumab (TH), trastuzumab-pertuzumab (HP) or docetaxel-pertuzumab (TP) combinations.
- Efficacy results are most pronounced in ER- and PR-negative tumors.
- Excellent tolerability of the combination regimen of THP.
- There is no appreciable increase in cardiac risk with the addition of pertuzumab to TH combination over a short course of neoadjuvant therapy.

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

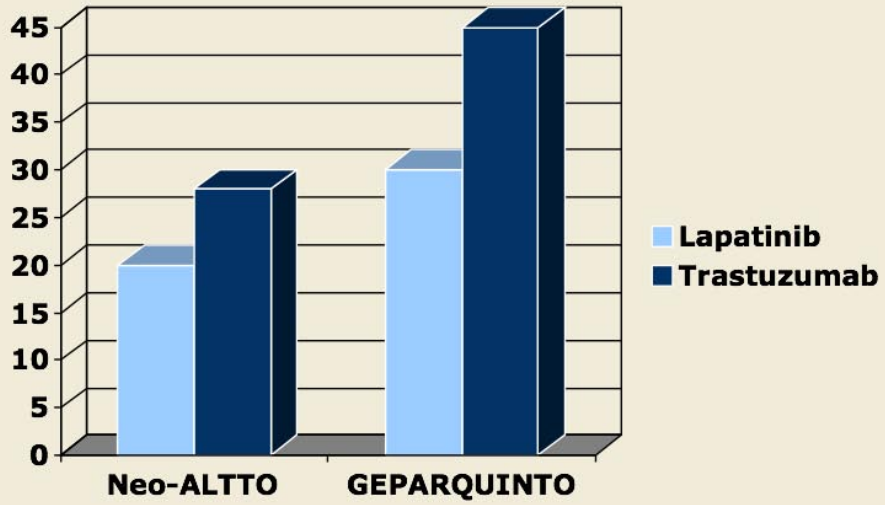
Research To Practice®

Neoadjuvant Therapy for HER2+ Breast Cancer

Winer E.
Proc SABCS 2010;Discussant.

Research To Practice®

Pathologic CR Trastuzumab/Chemo vs Lapatinib/Chemo

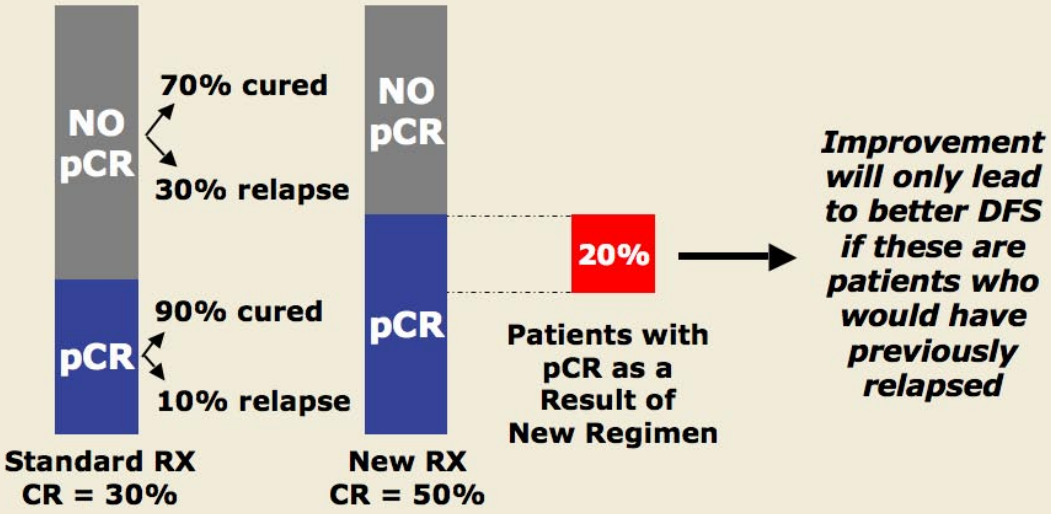


Inability to give planned doses of lapatinib ~35% in both studies.

Winer E. Discussant. *Proc SABCS* 2010.

Research To Practice®

Will Pathologic Response Predict Long-Term Outcome?



Winer E. Discussant. *Proc SABCS* 2010.

Research To Practice®

What Can Be Accomplished in the Neoadjuvant Setting?

- Identification of promising treatment strategies for patients at high risk of recurrence
- Identification of patients who may fare well with less toxic treatment
  - Single-agent chemotherapy + biologic therapy
  - Biologic therapy alone
- Interrogation of tissue for molecular predictors of outcome
- Discovery of new targets

Winer E. Discussant. *Proc SABCS* 2010.

Research To Practice®

The Score Card: What's Up and What's Down?

↑ **Trastuzumab + lapatinib with paclitaxel**	***Not ready for adjuvant or neoadjuvant use yet, but eagerly await ALTTO***
↑ **Trastuzumab + pertuzumab with docetaxel**	***Ready for adjuvant trial (Non-chemo containing doublet should move forward)***
↓ **Lapatinib alone + chemo**	***Appears a little less active and more toxic. Jury out until ALTTO results in.***
↓ **Pertuzumab alone + chemo**	***Hard to get excited***

Winer E. Discussant. *Proc SABCS* 2010.

Research To Practice®

Investigator Commentary: NeoSphere Neoadjuvant Trial

The triplet combination of docetaxel/trastuzumab and pertuzumab is associated with a very high pathological complete response (pCR) rate of 46 percent in the breast, which is significantly higher than the pCR rate of 29 percent with conventional treatment of docetaxel and trastuzumab achieved in our trial. The pCR rate for pertuzumab and chemotherapy was 24 percent, and interestingly we observed a pCR rate of about 17 percent with the pertuzumab/trastuzumab combination alone.

NeoSphere establishes that the addition of pertuzumab to a conventional regimen of chemotherapy/trastuzumab provides additional benefit for women with HER2-positive breast cancer, which justifies the conduct of an adjuvant trial evaluating this combination. Additionally, the activity observed with the combination of trastuzumab/pertuzumab without chemotherapy justifies continuing the doublet monoclonal antibodies together for 12 months after completion of chemotherapy without risk of incurring an increase in toxicity. As a result of NeoSphere, the Breast International Group will launch such an adjuvant trial by the end of 2011.

Interview with Luca Gianni, MD, December 10, 2010

Research To Practice®