5 Minute JournalClub

Key SABCS Presentations

Issue 1, 2011

Trastuzumab or Lapatinib with Neoadjuvant Chemotherapy in the Management of Previously Untreated HER2-Positive Primary 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. 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

- Apply the results of new research when recommending neoadjuvant chemotherapy with anti-HER2 treatment to patients with untreated HER2-positive primary breast cancer.
- Recognize the contribution of agent-specific toxicities to the rate of overall compliance with neoadjuvant anti-HER2 therapy.

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No real or apparent conflicts of interest to disclose.

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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.

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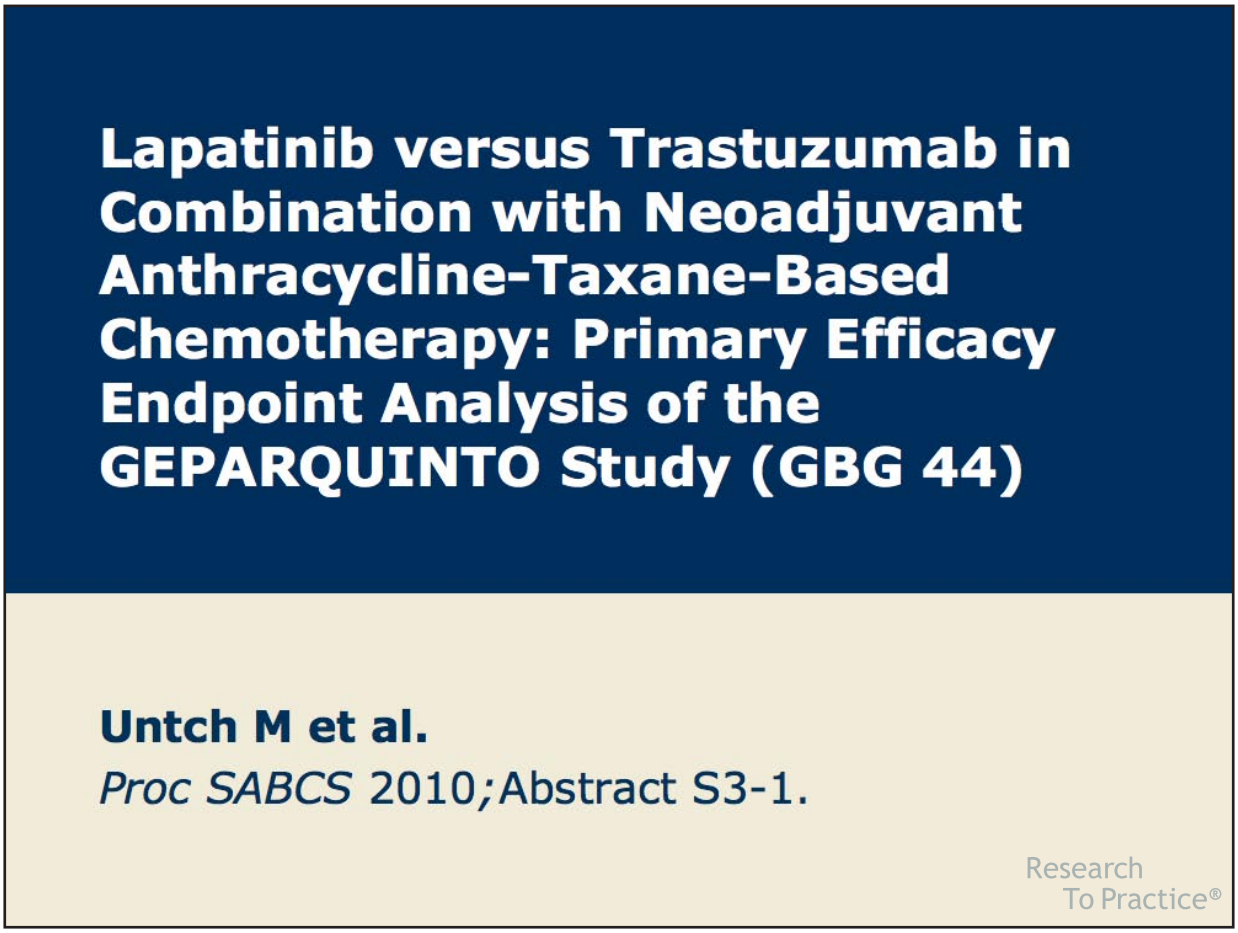
Trastuzumab or Lapatinib with Neoadjuvant Chemotherapy in the Management of Previously Untreated HER2-Positive Primary Breast Cancer

Presentation discussed in this issue

Untch M et al. **Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44).** San Antonio Breast Cancer Symposium 2010;**Abstract S3-1**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Michael Untch, MD, PhD (12/11/10)



Objectives

- Primary: Pathological CR rates
- Secondary:
  - Pathological CR rates with alternate definitions of pathological CR
  - Breast conservation rate
  - Compliance and toxicity
  - Efficacy in stratified risk groups
  - Disease-free and overall survival

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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Eligibility

- Untreated primary breast carcinoma
- HER2-positive by local pathology (IHC score 3+ or FISH+)
- Tumor stages:
  - cT4 or cT3
  - cT2 if HR- or cN+
  - cT1 if HR- or if SLN+
- Breast lesion ≥ 2 cm by palpation or ≥ 1 cm by ultrasound
- No metastasis
- Normal organ function
- Left ventricular ejection fraction ≥ 55%

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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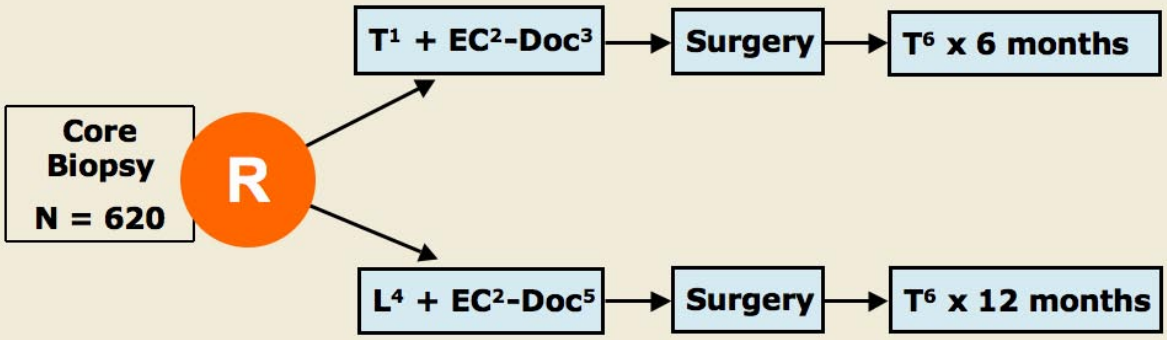
Study Schema



[1] Trastuzumab (T) 6 mg/kg q3wk x 8 (initial loading dose 8 mg/kg)
[2] Epirubicin (E) 90 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 q3wk x 4
[3] Docetaxel (Doc) 100 mg/m^2 q3wk x 4
[4] Lapatinib (L) 1,000-1,250 mg PO QD
[5] Doc 100 mg/m^2 q3wk (with G-CSF support) x 4
[6] T 6 mg/kg q3wk

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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Efficacy Results

	T + EC-Doc	L + EC-Doc	*p*-value
Pathological CR (no invasive or noninvasive residual in breast and nodes based on central pathology report review)	31.3%	21.7%	< 0.05
Pathological CR (no invasive residual in breast and nodes according to other definitions)	45.0%	29.9%	< 0.05
Pathological CR (no invasive residual in breast only according to other definitions)	50.4%	35.2%	< 0.05
Breast conservation rate	65.6%	56.0%	—

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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Efficacy Results by Stratification

	Odds Ratio
Overall	0.61
ER/PR-negative	0.63
ER/PR-positive	0.56
T1-3 and N0-2	0.54
T4 or N3	0.97

A lower odds ratio suggests results favorable to T + EC-Doc vs L + EC-Doc.

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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Safety and Compliance Results

	T + EC-Doc	L + EC-Doc
Discontinued chemotherapy + anti-HER2 agent	10%	16%
Discontinued anti-HER2 agent only	3.1%	7.0%
Serious adverse events	13.5% (T + EC) 14.5% (T + Doc)	17.7% (L + EC) 15.2% (L + Doc)

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

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Conclusions

- Trastuzumab + EC-docetaxel achieved a significantly higher pathological CR rate in unselected HER2-positive primary breast cancer when compared to the lapatinib combination with the same chemotherapy.
- Efficacy results were consistent in most prespecified subsets, including ER/PR-negative and ER/PR-positive subtypes.
- Compliance of lapatinib with EC-docetaxel was lower than trastuzumab plus EC-docetaxel.
- Results should be seen in the context of other studies like Neo-ALTTO, which uses a higher dose of lapatinib (1,500 mg/d), but a shorter treatment duration.

Untch M et al. *Proc SABCS* 2010;Abstract S3-1; Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Investigator Commentary: GEPARQUINTO Neoadjuvant Study (GBG 44)

GEPARQUINTO is the first clinical trial to compare chemotherapy/trastuzumab with chemotherapy/lapatinib. According to NSABP criteria, the pCR was 50 percent with chemotherapy/trastuzumab and 35 percent with chemotherapy/lapatinib, which was unexpectedly lower than was hypothesized at the beginning of this study.

In the intention-to-treat analysis 23 percent of patients in the chemotherapy/lapatinib arm had treatment discontinued due to Grade III and higher diarrhea compared to a 13 percent rate of discontinuation in patients who received chemotherapy/trastuzumab. This was the first time that lapatinib has been administered with anthracyclines and docetaxel, and we had to learn how to cope with the side effects of this combination. We learned that it was necessary to reduce the dose of lapatinib from 1,250 mg to 1,000 mg to avoid the diarrhea, and we also learned to add G-CSF to avoid febrile neutropenia from lapatinib and docetaxel. These are important lessons learned from this trial, and we now discuss with patients which side effects to expect and how to deal with them.

Interview with Michael Untch, MD, PhD, December 11, 2010