



**Updated Survival Analysis of the
EGF104900 Randomized Study
of Lapatinib Alone or Combined
with Trastuzumab for HER2-Positive
Breast Cancer Progressing
on 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. 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 where 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 OBJECTIVE

- Summarize the updated results for survival and safety from the randomized study of lapatinib alone or in combination with trastuzumab for HER2-positive metastatic breast cancer that has progressed on trastuzumab.

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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:

Mark D Pegram, MD
Full Professor of Medicine
Director for the Translational Research Program
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IN THIS ISSUE:

- [Trastuzumab/lapatinib](#) demonstrates survival advantage in metastatic HER2-positive breast cancer
- [Adjuvant therapy](#) in patients with small node-negative, HER2-positive tumors
- [Trastuzumab/TC](#) as adjuvant therapy

Shortly before the recent Pro Bowl in Miami, our CME group hosted a marquee event of our own about ten minutes from the stadium as nine breast cancer “all stars” came together in our sound studio for a daylong think tank audio recording. It’s not surprising that my mental highlight film from the meeting includes many innovative ideas and poignant comments by the soft-spoken and super-smart Harvard maven, Dr Paul Goss.

In a follow-up audio interview with Paul, he thoughtfully discussed several patients from his practice. The case that stood out for me was a 38-year-old woman who came for a second opinion after having received several different chemo/anti-HER2 regimens for metastatic disease. This patient’s original primary tumor was ER-positive, HER2-positive, but on recurrence a vertebral biopsy revealed HER2-positive, ER-negative disease, and she had not received endocrine therapy since the disease recurred.

According to Paul, at this point the woman was sick and tired of being sick and tired of chemo, which in part prompted his highly interesting and somewhat unusual treatment recommendation of the combination of letrozole, trastuzumab and lapatinib, an innovative biologic triplet that makes a lot more sense since Kim Blackwell’s stunning [San Antonio presentation](#) profiled in our slide set, which compared lapatinib to trastuzumab/lapatinib in patients with heavily pretreated metastatic disease. Her presentation was an update of the data that were just published in the *Journal of Clinical Oncology*.

Listening to Paul’s case, I was particularly interested in his explanation for using endocrine therapy in spite of a recent ER-negative biopsy, which was based on his concern about the possibility of sampling error particularly because the tissue biopsied was bone, which he feels is ripe for inaccuracies. An equally important factor in his recommendation is the relative lack of toxicity with hormone therapy and the recent data supporting the addition of anti-HER2 therapy to up-front endocrine treatment of metastatic disease. Paul and others believe that anti-HER2 treatment may potentiate

endocrine therapy by a variety of mechanisms including interference with ligand-independent ER activation.

In terms of the HER2 part of this interesting triplet, Paul, like most San Antonio attendees, was very impressed with the trastuzumab/lapatinib data set — one of the very few recent trials to demonstrate a survival benefit in metastatic disease in spite of a built-in crossover design. Dr Goss believes part of the explanation for this finding is that these patients had received so many prior therapies that post-trial intervention had less impact. Another important principle borne out by this study is the potential benefit of continuing trastuzumab beyond disease progression, which was previously supported by the German trial of trastuzumab/capecitabine in patients with disease progression on trastuzumab with other chemo agents. During the think tank, the faculty commented on the sea change in approach to patients with metastatic HER2-positive disease that resulted from this study and the trastuzumab/lapatinib trial in which continuous anti-HER2 therapy has quickly become routine clinical practice.

Although many viewed the recent Pro Bowl as a sham in which the participants seemingly could have cared less about the outcome, I smile inwardly reflecting on a pretty amazing day with Paul and our other “All Pro” investigators. The intriguing clinical and laboratory science discussed that “Super” day suggests that the biology of this disease is finally coming together in a way that maybe will soon have a meaningful impact on patient care.

Next up on 5-Minute Journal Club: San Antonio excitement on bone-targeted therapy.

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Updated Survival Analysis of the EGF104900 Randomized Study of Lapatinib Alone or Combined with Trastuzumab for HER2-Positive Breast Cancer Progressing on Trastuzumab

Presentation discussed in this issue

Blackwell KL et al. **Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy.** San Antonio Breast Cancer Symposium 2009; **Abstract 61**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Mark D Pegram, MD (12/23/09)

Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy

Blackwell KL et al.
SABCS 2009;Abstract 61

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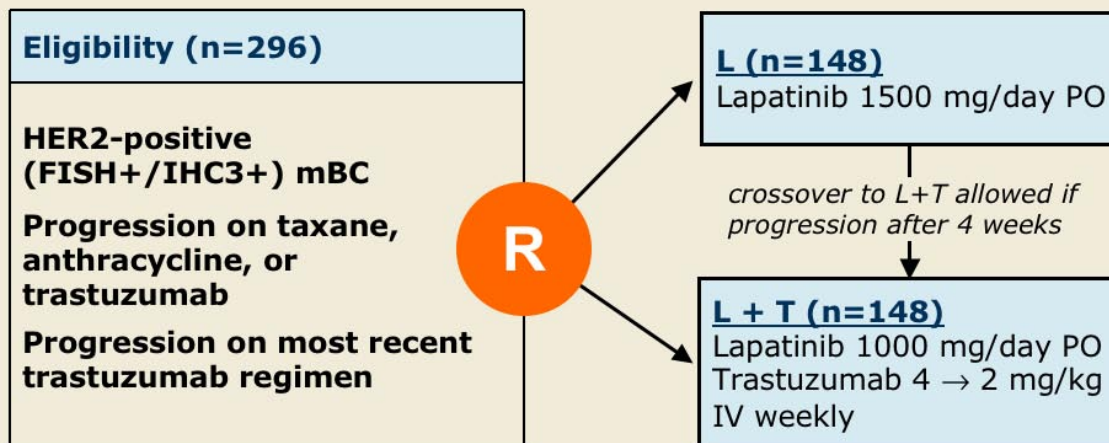
Introduction

- Synergy between lapatinib (L) and trastuzumab (T) has been established in preclinical models (*Cancer Res* 2006;66:1630).
- Phase III trial EGF104900 compared L + T versus L alone in patients with HER2+ metastatic breast cancer (mBC) who progressed on multiple lines of trastuzumab-based therapy (ASCO 2008;Abstract 1015).
 - Significant improvement in progression-free survival (PFS) at 6 months and in the clinical benefit rate (CBR) were demonstrated:
 - PFS: 28% (L+T) vs 13% (L)
 - CBR: 24.7% (L+T) vs 12.4% (L)
 - Trend toward overall survival (OS) favoring L+T was shown.
- **Current Study Objectives**
 - Provide updated EGF104900 study results with final intent-to-treat OS analysis and cardiac and safety event data.

Blackwell KL et al. SABCS 2009;Abstract 61.

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EGF104900: Phase III Study of Dual HER2 Blockade

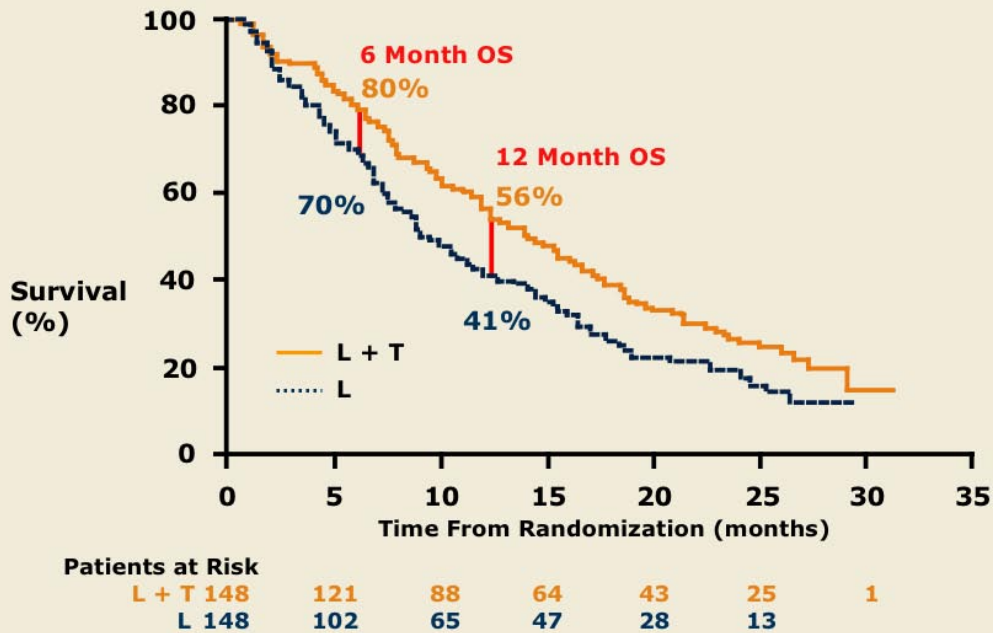


*Staging at 4, 8, 12, 16 weeks, then every 8 weeks
Steady state of single-agent lapatinib occurs at ~7 days*

Blackwell KL et al. SABCS 2009;Abstract 61.

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Updated Overall Survival in ITT



With permission Blackwell KL et al. SABCS 2009;Abstract 61.

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EGF104900: Final Survival Analysis

	L + T (n=146)	L (n=145)
Events, n (%)	105 (72)	113 (78)
Median Survival (months)	14	9.5
Hazard ratio (95% CI)	0.74 (0.57, 0.97)	
Log-rank <i>p</i> -value	0.026	

Factors influencing overall survival (from COX proportional hazard analysis):

- Treatment assignment
- ECOG performance status
- Disease site
- Number of metastatic sites
- Time from first or initial diagnosis of BC until randomization

Blackwell KL et al. SABCS 2009;Abstract 61.

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EGF104900: Updated Cardiac and Safety Events

	L + T (n=149)	L (n=146)
Total number of patients with event	11 ^a	3
Grade 3/4 events, n (%)	3 (2)	1 (<1)
Serious events ^b , n	10	3
Events related to study drug(s), n	10	2
Deaths (n) ^c	1	0

^aTwo patients experienced 2 events (other event was Grade 1/2)

^bLV dysfunction \geq Grade 3 or LVEF decrease \geq 20% from baseline + < LLN

^cCardiac failure; cause of death: pulmonary thromboembolism

- Majority of AEs with \geq 10% incidence were Grade 1/2
- Grade 3/4 AEs with \geq 5% incidence: Diarrhea (8% L+T; 7% L)

Blackwell KL et al. SABCS 2009;Abstract 61.

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Conclusions

- Treatment with L + T resulted in a 26% reduction in the risk of death ($p=0.026$) for patients with HER2+ mBC with disease progression on trastuzumab.
- Survival benefit was observed despite a 52% crossover of patients from single-agent L to combination therapy at progression (data not shown).
- Tolerability profile of combined L+T was acceptable, with no observed increase in cardiac signal.
- Trial results lend support and evidence for the ongoing Phase III ALTTO trial that will examine adjuvant T and L monotherapy, T followed by L, and L+T combination therapy for patients with HER2-amplified BC.

Blackwell KL et al. SABCS 2009;Abstract 61, www.ClinicalTrials.gov (January 2010) Research
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DR PEGRAM: Kim Blackwell presented an update of a study that was presented at ASCO 2008, evaluating lapatinib with or without trastuzumab in women with HER2-positive metastatic breast cancer who experience disease progression on trastuzumab therapy.

The rationale for this study design was based on my work at UCLA with Gottfried Konecny. We performed a series of experiments on the combination of trastuzumab plus lapatinib, expecting antagonism between the two agents since they hit the same target. To our surprise, what we measured was synergism between them. The purpose of this Phase III trial was to see if there would be any basis for exploiting this synergy in the clinic.

Previously, statistically significant improvement of progression-free survival (PFS) was shown in the intent-to-treat population. At the six-month mark, it went from 13 percent to 28 percent in favor of the combination, and the median PFS went from 8.1 to 12 weeks.

This trial was conducted in a heavily pretreated population of patients with HER2-positive breast cancer and a median of three prior trastuzumab-containing regimens for metastatic disease. Patients whose disease progressed on their most recent trastuzumab-containing regimens were randomly assigned to lapatinib alone or lapatinib plus continued trastuzumab.

In our Phase I dose-escalation and pharmacokinetic study of lapatinib in combination with trastuzumab, we arrived at the lapatinib dose used in this trial. In the Phase I study, we saw some dose-limiting toxicity in the form of fatigue at the highest doses, so we backed off to lapatinib 1,000 mg per day.

One-month improvement in PFS is not a lot to get excited about, but it's a signal. Usually when you see such a fairly modest signal in PFS, you don't expect that it's going to translate into a survival benefit, especially not with an "N" of about 150 per arm. This was a study with very limited statistical power to critically evaluate a survival endpoint, especially in such a heavily pretreated population.

It was not expected to see any signal here with respect to the overall survival analysis. Surprisingly, Dr Blackwell showed a statistically significant improvement in overall survival in the intent-to-treat population, with a median increase from 9.5 to 14 months and a *p*-value of 0.026.

The improvement in overall survival is amazing. In a heavily pretreated metastatic breast cancer population, I can't recall a single study in the history of any agent or combination of agents that's ever shown a survival benefit.

In this trial, 52 percent of the patients in the lapatinib alone arm crossed over to the combination. I've seen the Kaplan-Meier survival plots of only the patients who did not cross over, and they are miles apart. To me, that implies there's something

unique about this combination. No one can rule out the possibility that just continuing trastuzumab might be associated with some efficacy, but I doubt it would have impacted survival after a failure of a median of three prior trastuzumab-containing regimens for metastatic disease.

Will these data foreshadow the results of the ongoing Neo-ALTTO and ALTTO studies? These trials are head-on comparisons of lapatinib versus trastuzumab versus the combination in the neoadjuvant and adjuvant settings. Based on what we're seeing, either this is a wild statistical fluke or the combination will in fact prove to be superior in those ongoing studies.

Dr Pegram is Full Professor of Medicine and Director for the Translational Research Program at the Braman Family Breast Cancer Research Institute at UM Sylvester Comprehensive Cancer Center in Miami, Florida.