



**EGF30008: Evaluation of
Biomarkers in a Study of Letrozole
with or without Lapatinib in
ER-Positive Metastatic Breast Cancer**

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting more than 30,000 attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Recognize biomarkers that may aid in the identification of patients with hormone receptor-positive metastatic breast cancer likely to benefit from the addition of lapatinib to aromatase inhibitor therapy.

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Click to go directly to our slides and comments on [pazopanib in renal cell cancer](#), [use of endocrine therapy plus lapatinib in breast cancer](#) and [two key ASCO papers on imatinib in GIST](#).

This summer, for the second straight year, our CME group held a daylong clinical investigator think tank on renal cell carcinoma (RCC) in our recording studio in Miami — pretty amazing considering that just four or five years ago we would have likely been done in an hour and could have gone to the beach.

Nowadays there is a lot to talk about in RCC, and in planning this meeting with Co-Chair Bob Figlin, one of our main objectives was to see if there was consensus among the faculty about a new and emerging paradigm in this disease. Specifically we were interested in the issue of dose intensity with VEGF TKIs (sunitinib or sorafenib), and whether patients generally receive the planned dose and schedule of these agents in community-based practice — an idea that we heard about for years in various settings related to chemotherapy.

The renal investigators uniformly supported this concept in the advanced disease setting and believe — although it's not clear how much data we have on this — that the usual duration of therapy, specifically with the widely accepted first-line treatment, sunitinib, is significantly shorter in community-based practice than was reported in the major studies of the agent and by investigators in their practices. This has created concern that patients may experience suboptimal treatment benefit because physicians "bail out" or reduce the dose early without attempting to proactively manage side effects.

The issue of planned dose and schedule and the often challenging side effects of these treatments greatly increase the significance of ongoing research evaluating other similar agents with perhaps less toxicity and theoretically more leeway to keep therapy in the "area under the curve." At ASCO we heard more encouraging data about pazopanib, a VEGF TKI with a different and perhaps more favorable tolerability profile than sunitinib with hopefully similar or equivalent efficacy. An ongoing Phase III trial will compare pazopanib to sunitinib, and hopefully answer this critical question.

Please click here for our slides and commentary on [pazopanib in renal cell cancer](#).

The next stop on our TKI update is breast cancer, and an interesting study first presented at San Antonio 2008 and updated at ASCO, re-examining an issue previously

studied in the so-called TAnDEM trial — optimal first-line systemic therapy for postmenopausal patients with ER-positive, HER2-positive metastatic breast cancer.

TAnDEM compared anastrozole alone or with trastuzumab, and the more recent EGF30008 study compared letrozole alone or with lapatinib. Although TKIs, as noted in the renal think tank, pose considerable challenges in administration, the quality-of-life advantage of an all-oral, endocrine/HER2 blockade offers patients facing a limited life span more time at home and other important places.

Please click here for slides and commentary on the [**use of endocrine therapy plus lapatinib in breast cancer**](#).

Finally, we focus on the shining star of all TKIs, imatinib, and while the results in GIST are not as magical as they are with CML, this agent and others offer hope to patients who a decade ago weren't even identified within the sarcoma classification schemes. Two ASCO reports reviewed by GIST maven Charles Blanke provide important new findings on the impact of discontinuing imatinib in patients with advanced disease, and the suggestion that prolonged or indefinite therapy may be optimal.

Please click here for slides and commentary on [**two key ASCO papers on imatinib in GIST**](#).

Next up on 5-Minute Journal Club: A quartet of breast cancer reports, and snippets from another amazing think tank, including a stand-off on one of the most compelling questions in medical oncology: Does adjuvant trastuzumab offer treatment benefit to patients with HER2-negative tumors?

[**Please click here**](#) to receive immediate notification and a link to download our Renal Cell Think Tank when it's published or to receive the program in hard copy with audio CDs.

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EGF30008: Evaluation of Biomarkers in a Study of Letrozole with or without Lapatinib in ER-Positive Metastatic Breast Cancer

Presentations discussed in this issue:

Finn RS et al. **Progression-free survival (PFS) of patients with HER2-negative, estrogen-receptor (ER)-low metastatic breast cancer (MRC) with the addition of lapatinib to letrozole: Biomarker results of EGF30008.** *Proc ASCO* 2009; **Abstract 1018**. (Poster discussion)

Platek GT et al. **Relevance of serum HER2 extracellular domain (sECD) in EGF30008, a study of letrozole ± lapatinib in patients (pts) with hormone-receptor positive (HR+) metastatic breast cancer (MBC).** *Proc ASCO* 2009; **Abstract 1019**. (Poster discussion)

Slides from the presentations and excerpts from a related “Journal Club” (January 22, 2009) featuring Eleftherios P Mamounas, MD, MPH, Sandra M Swain, MD and Antonio C Wolff, MD

Progression-Free Survival (PFS) of Patients with HER2-Negative, Estrogen-Receptor (ER)-Low Metastatic Breast Cancer (MBC) with the Addition of Lapatinib to Letrozole: Biomarker Results of EGF30008

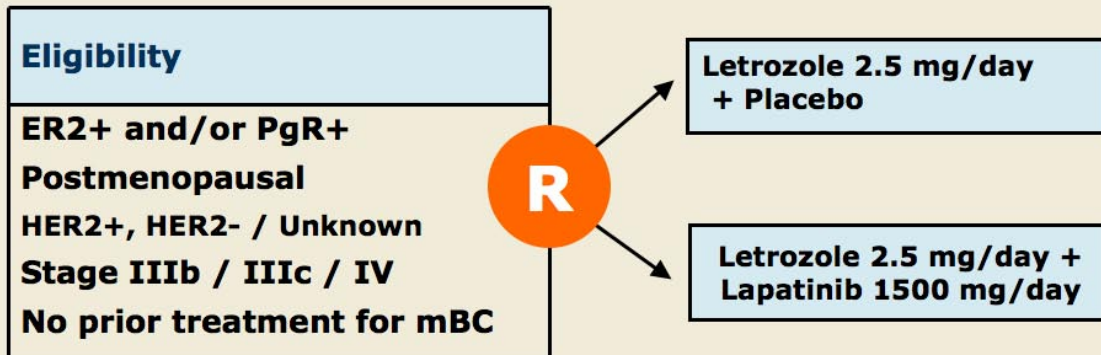
Finn RS et al.

American Society of Clinical Oncology
2009; Abstract 1018. (Poster Discussion)

Background: EGF30008

Protocol ID: EGF30008

Accrual: 1286 (including n = 219 HER2+)



Stratification factors:

Disease sites

- Bone only / visceral or soft tissue

Interval since adjuvant tamoxifen

- < 6 mos / ≥ 6 mos or more

Source: Johnston S et al. *SABCS 2008*; Abstract 46.

Summary of EGF30008 Results 2008 San Antonio Breast Cancer Symposium

- In postmenopausal women with HR+, HER2+ mBC the combination of letrozole and lapatinib previously demonstrated:
 - Reduction in risk of disease progression – 29% (p = 0.019)
 - Improvement in median PFS from 3.0 to 8.2 months
 - Significant improvement in clinical benefit rate from 29% to 48% (p = 0.003)
- In postmenopausal women with HR+, HER2- mBC:
 - No significant PFS treatment benefit (HR 0.90; p = 0.188)
 - Reduction in risk of disease progression (by preplanned Cox analysis [adjusted treatment HR 0.77, p = 0.010])
 - Prior tamoxifen exposure was significant covariate
 - Biomarker studies ongoing to further define HR+, HER2- population that may benefit

Source: Johnston S et al. *SABCS 2008*; Abstract 46.

Introduction: Biomarker Study

- Rationale for the combination of lapatinib and letrozole in metastatic breast cancer (mBC):
 - Interaction of peptide growth factor- and hormonal-signaling plays a role in breast cancer etiology and progression (Clin Cancer Res 2008;14:4484)
 - Prior studies with EGFR-targeted agents suggested a relationship between HR status (estrogen receptor [ER] and progesterone receptor [PR]) and response to HER-directed therapies
 - Lower, but not absent, HR expression may indicate stronger tumor addiction to peptide growth factor pathway (J Clin Oncol 2009 Epub Ahead of Print)
- EGF3008 (N = 1,286) Phase III trial primary efficacy results:
 - HR-pos, HER2-pos/neg/unknown MBC randomized to letrozole + lapatinib or placebo
 - Primary endpoint: PFS in HR-pos HER2-pos
 - 8.2 mos vs 3 mos (p=0.019) favoring combination
 - No benefit in HER2-neg
 - 13.7 mos vs 13.4 mos (p=0.188)

Source: Finn RS et al. ASCO 2009; Abstract 1018.

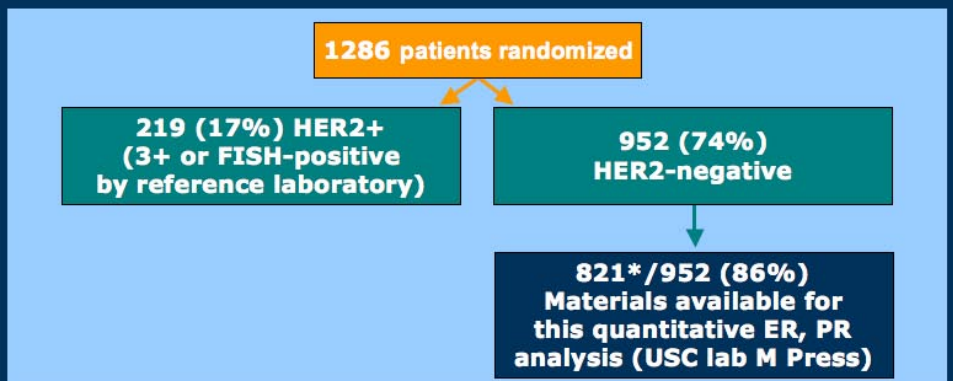
Introduction (continued)

- **Current study objectives of blinded biomarker analysis of EGF3008:**
 - Central laboratory analysis of archived tumor tissue for HER2 (IHC and/or FISH) and ER/PR status
 - Semiquantitative measurement of HR status with calculation of “H-score” for ER and PR
 - H-score = (% of sample staining 1+ intensity x 1) + (% of sample staining 2+ intensity x 2) + (% of sample staining 3+ intensity x 3);
Maximum H-score = 100% 3+ x 3 = 300
 - Correlation of biomarkers with clinical outcome

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Central Biomarker Assessment

Available data



***Note: 19 patients that were ER-negative in central review were excluded.**

N = **821 HER2-negative** tumor samples underwent quantitative ER/PR analysis:
ER and PR subgroups were analyzed by H-score quartiles

Quartile 1: Low

Quartiles 2 and 3: Intermediate

Quartile 4: High

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Results: PFS by ER Quartile, HER2-Negative MBC

	Letrozole + Lapatinib	Letrozole + Placebo	HR (95% CI)	p value
ER Quartile 1 (Low H-score <160) (n = 109, 97)	13.6 mos	6.7 mos	0.65 (0.47-0.90)	0.01
ER Quartiles 2 and 3 (Intermediate H-score ≥160 and <250) (n = 195, 194)	13.6 mos	14.2 mos	0.96 (0.75-1.23)	0.77
ER Quartile 4 (High H-score ≥250) (n = 114, 112)	11.2 mos	14.2 mos	0.96 (0.75-1.23)	0.58

Patients treated with letrozole + lapatinib with low ER expression had a significant benefit from the addition of lapatinib vs placebo

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Results: PFS by PR Quartile, HER2-Negative MBC

	Letrozole + Lapatinib	Letrozole + Placebo	HR (95% CI)	p value
PR Quartile 1 (Low H-score <40) (n = 114, 99)	11.2 mos	8.0 mos	0.65 (0.47-0.90)	0.20
PR Quartiles 2 and 3 (Intermediate H-score ≥40 and <220) (n = 189, 199)	13.6 mos	13.6 mos	0.98 (0.77-1.25)	0.83
PR Quartile 4 (High H-score ≥220) (n = 115, 105)	17.4 mos	16.6 mos	0.87 (0.62-1.22)	0.43

Strength of PR expression did not correlate with outcome from the addition of lapatinib to letrozole

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Results: PFS by Time Since Prior Hormonal Therapy and Treatment, HER2-Negative MBC

Prior Hormonal Therapy	Letrozole + Lapatinib	Letrozole + Placebo	HR (95% CI)	p value
< 6 months elapsed (n = 88, 91)	9.4 mos	3.0 mos	0.74 (0.53-1.05)	0.09
≥ 6 months elapsed (n = 113, 104)	11.1 mos	13.2 mos	0.98 (0.71-1.35)	0.89
No prior hormonal therapy (n = 217, 208)	16.4 mos	16.3 mos	0.98 (0.77-1.25)	0.85

There was a trend for patients who discontinued tamoxifen <6 months prior to enrollment to benefit from the addition of lapatinib to letrozole

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Summary and Conclusions

- For patients with HER2-negative ER-positive mBC with documented low ER expression (ER H-score <160), the addition of lapatinib to letrozole significantly improves PFS
 - 13.6 vs 6.7 months ($p = 0.01$)
- Quantitative PR expression did not correlate with benefit from letrozole + lapatinib
- Patients with a short relapse time since adjuvant tamoxifen experienced a trend toward improved PFS with addition of lapatinib ($p = 0.09$)
 - No correlation between low ER expression and short relapse time (data not shown)
- This study builds on data suggesting link between low HR expression and peptide growth factor dependence

Source: Finn RS et al. ASCO 2009; Abstract 1018.

Relevance of Serum HER2 Extracellular Domain (sECD) in EGF30008, a Study of Letrozole ± Lapatinib in Patients (pts) with Hormone-Receptor Positive (HR+) Metastatic Breast Cancer (MBC)

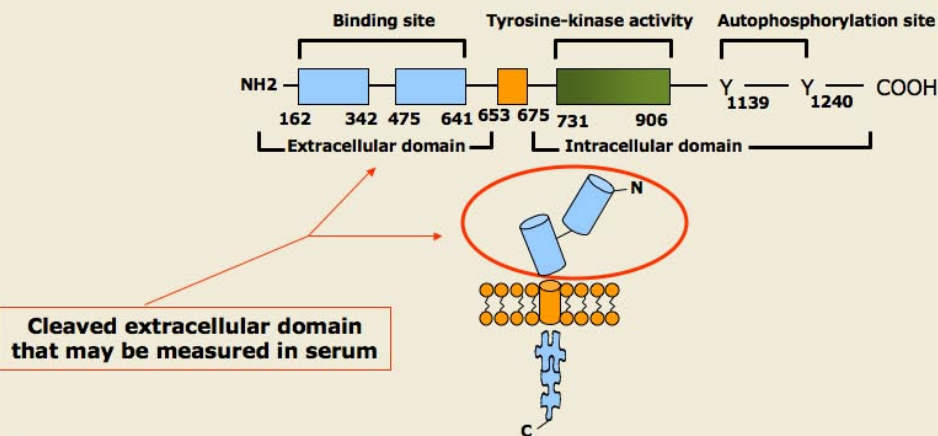
Platek GT et al.

American Society of Clinical Oncology
2009; Abstract 1019. (Poster Discussion)

Introduction

- The p185kDa portion of the HER2 receptor can be proteolytically cleaved leaving a p95kDa membrane-bound fragment (p95HER2) and a p97-115kDa extracellular domain (ECD) that can be accurately measured in the serum (sECD)

HER2 Protein: Schematic



Source: Atlas of Genetics and Cytogenetics in Oncology and Hematology.
<http://AtlasGeneticsOncology.org>.

Introduction

- sECD >15 ng/mL is an independent risk factor for shortened survival and is associated with worse survival after disease recurrence
- Current study objectives:**
 - Exploratory analysis to assess the effect of sECD (baseline and on-treatment) and HER2 tissue status on PFS in patients with HR-positive mBC enrolled in the EGF30008 study (letrozole + lapatinib vs letrozole + placebo)
 - Correlate baseline sECD (positive: >15 ng/mL) with HER2 status by IHC and FISH
 - Determine the effect of baseline sECD on PFS in the HER2-positive and HER2-negative populations
 - Assess rate of sECD seroconversion by treatment arm and the impact of seroconversion on PFS

Source: Platek GT et al. ASCO 2009; Abstract 1019.

Progression-Free Survival (PFS) According to HER2 and Baseline sECD Status

	Baseline sECD High (>15 ng/mL)		Baseline sECD Low (≤15 ng/mL)	
	HR* (95% CI)	p-value	HR* (95% CI)	p-value
Tissue <u>HER2-positive</u> : PFS by baseline sECD (n= 87, 121)	0.44 (0.29-0.69)	<0.001	1.06 (0.70-1.62)	0.773
Tissue <u>HER2-negative</u> : PFS by baseline sECD (n= 125, 769)	0.93 (0.62-1.39)	0.720	0.84 (0.70-1.00)	0.046

* HR < 1.0 favors letrozole + lapatinib vs letrozole + placebo

Source: Platek GT et al. ASCO 2009; Abstract 1019.

Rate of sECD Seroconversion

	Risk ratio	Letrozole 2.5 mg + 1500 mg Lapatinib (n = 478)	Letrozole 2.5 mg + Placebo (n = 474)	Total (N = 952)
Seroconverter disposition	At risk*	359	375	734
Seroconversion rate		61% (219/359)	14% (52/375)	37% (271/734)

*At risk patients were tissue-negative and serum HER2-negative at baseline with at least 1 serum HER2 measurement while on treatment

Rate of seroconversion is >4 fold higher on lapatinib arm vs placebo

Source: Platek GT et al. ASCO 2009; Abstract 1019.

Summary and Conclusions

- Baseline sECD is weakly but statistically correlated with tissue HER2 status by IHC and FISH (data not shown)
- HER2-positive and baseline high sECD (n=87) population experienced significantly longer PFS (24.1 vs 11.7 wks; HR: 0.44; $p < 0.001$) with addition of lapatinib
 - Same effect not observed in HER2-negative population with baseline high sECD
- Rate of sECD seroconversion from negative (low) to positive (high) was significantly higher among patients treated with lapatinib
 - However, seroconversion did not have an effect on PFS; thus limiting the clinical utility of sECD in this study

Source: Platek GT et al. ASCO 2009; Abstract 1019.

DR ANTONIO C WOLFF: The study that Steve Johnston presented (EGF30008) was a randomized Phase III clinical trial in which patients with hormone receptor-positive, HER2-positive or HER2-negative, metastatic breast cancer were treated with letrozole with or without lapatinib. The primary endpoint was progression-free survival in the patients with HER2-positive disease. The patients were allowed to have prior adjuvant tamoxifen or not and were stratified on the basis of the interval since prior adjuvant tamoxifen.

They reported significant improvement in the progression-free survival in the HER2-positive population, with a hazard ratio of 0.71. There was also an improvement in the response rate and what they call “the clinical benefit ratio” in patients with HER2-positive tumors when they received the combination of lapatinib and letrozole versus letrozole alone. In terms of overall survival, there was a trend — a hazard ratio of 0.74 — for improvement with the addition of lapatinib. For the HER2-negative population, there was no benefit.

DR NEIL LOVE: Sandy, we had previous data looking at trastuzumab with anastrozole. How do you approach first-line therapy for patients with an ER-positive, HER2-positive tumor?

DR SANDRA M SWAIN: This study with lapatinib and letrozole reported a significant improvement in progression-free survival. So, based on this data, I would start

patients on hormonal therapy and lapatinib and watch them closely. In the TAnDEM study, patients progressed fairly rapidly. If that happened, then I would switch to chemotherapy and anti-HER2 therapy.

DR ELEFTHERIOS P MAMOUNAS: In EGF30008 and TAnDEM, I am impressed by how poorly patients fared with hormonal therapy alone if they have ER-positive, HER2-positive metastatic breast cancer. So it makes intuitive sense to use the anti-HER agent up front.

DR SWAIN: Quality of life is also important and if you can achieve a good benefit, such as in this study with lapatinib, then it would be worth attempting it before going to chemotherapy.

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