



Key SABCS Presentations
Issue 6, 2011

Concordance of HER2 Testing in Breast Cancer

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 OBJECTIVE

- Recognize the effect of round-robin adjudication and standardized assays on the resolution of discordant HER2 testing results between laboratories.

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[Click here for SABCS papers on HER2-positive breast cancer](#)



**View from Breast Cancer Think Tank toward Biscayne Bay and South Beach
7:30 AM February 4, 2011 (photo by Hope Rugo)**

In 2003, my CME compatriots and I moved out of our University of Miami offices with the goal of creating a unique environment that would inspire us and others to think differently about cancer treatment, research and education. We found a too-good-to-be-true sublease from a troubled bank in one of the oldest office buildings in South Florida with creepy "Tower of Terror" elevators but an unforgettable view. One of the ways we envisioned putting these cozy confines to good use would be to bring together clinical investigators, encourage a casual dress code and invite everyone to share what's most on their mind. At our recent breast cancer Think Tank, that is exactly what happened as Melody Cobleigh presented two very informative and interesting cases that have been occupying a significant amount of space in her head.

The first was a 25-year-old graduate student seeking another opinion for ER-negative, HER2-positive locally advanced breast cancer. At the Think Tank, the faculty agreed that chemo/trastuzumab was indicated and Dr Cobleigh relayed the good news that after one cycle of TCH most of the disease had receded. She then threw a wrench into the works by revealing that the repeat HER2 assay done at her institution was reported as negative (IHC 2+, FISH not amplified with a ratio of 1.2). Most of the faculty, including Dr Cobleigh, were nervous about discontinuing trastuzumab for obvious reasons, but there was also some sentiment in the other direction.

The other patient was a 58-year-old woman who had received adjuvant chemo and tamoxifen for an ER-positive, HER2-negative tumor that came roaring back in the form of extensive liver and bone mets. Dr Cobleigh ordered a liver biopsy that confirmed recurrence, but this time the tissue was read again as ER-positive but also HER2-positive. The patient went on to have a series of responses to anti-HER2 treatment alone or with chemo, but eventually she ran out of options and was rapidly deteriorating when a new trial became available using the immune conjugate T-DM1. Amazingly, this woman had a major tumor response and significant relief of symptoms, and much to everyone's surprise, at the time of the Think Tank she was hiking in Arizona on vacation. One can only imagine what the outcome might have been had Dr Cobleigh not obtained the liver biopsy and documented HER2-positive disease.

These patients are good examples of the increasing complexity, uncertainty and challenge associated with the management of HER2-positive breast cancer. In this issue of our series, we summarize a number of related reports from San Antonio that provide optimism, but also as many questions as answers about HER2-positive disease.

1. Two important papers on HER2 testing

These complicated and detailed studies analyzing tissue from patients enrolled in the ongoing ALTTO trial and previously reported adjuvant NCCTG and BCIRG trials demonstrate that Dr Cobleigh's patients are not rare, as some discordance in HER2 test results was seen even between central reference labs.

2. Adjuvant trastuzumab in older patients; long-term management of metastatic disease

A German report from a prospective observational study demonstrated comparable outcomes for "elderly" — defined as 65 and over — and younger patients receiving adjuvant trastuzumab. One might question the definition of elderly in this trial and wonder if data should be reported as in myeloma — above and below age 75 (the new 65). In any event, this study confirms what investigators have been saying for years — if fit older patients are managed carefully, they tolerate treatment well and derive similar benefit. The other papers provide more support that in metastatic disease, continuing anti-HER2 treatment indefinitely beyond progression adds benefit and is widely used in practice.

3. [More on T-DM1 and pertuzumab](#)

Based on a Dana-Farber study of 23 patients, Dr Cobleigh can anticipate that if and when her patient on T-DM1 develops progressive disease, further response to additional anti-HER2 treatment is likely. A future noncytotoxic option for HER2-positive disease might be the dual targeted approach reported in a Phase II study at San Antonio demonstrating that in 67 patients T-DM1 and pertuzumab can be combined and tolerated in full doses. Perhaps more importantly, the trial revealed a 57 percent objective response rate with this interesting combination in the first-line setting.

4. [Novel schedule of lapatinib/capecitabine](#)

Investigators at Memorial Sloan-Kettering have long been interested in the capecitabine schedule of seven days on, seven days off (7-7), and this Phase II study achieved encouraging results when capecitabine 7-7 was combined with daily lapatinib. A planned Phase III trial will compare the 7-7 schedule to the classic 14 days on, seven days off regimen.

Next up on *5-Minute Journal Club*: Several increasingly rare reports on adjuvant chemotherapy, including the role (or lack thereof) of adding in capecitabine.

Neil Love, MD

[Research To Practice](#)

Miami, FL

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Concordance of HER2 Testing in Breast Cancer

Presentations discussed in this issue

Perez EA et al. **Round-robin review of HER2 testing in the context of adjuvant therapy for breast cancer (NCCTGN9831/BCIRG006/BCIRG005)**. San Antonio Breast Cancer Symposium 2010; **Abstract PD10-02**.

McCullough AE et al. **Concordance of HER2 central assessment by two international central laboratories: A ring study within the framework of the adjuvant HER2-positive ALTTO trial (BIG2-06/N063D/EGF106708)**. San Antonio Breast Cancer Symposium 2010; **Abstract P3-10-36**.

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with William J Gradishar, MD (1/4/11)

**Round-Robin Review of HER2 Testing
in the Context of Adjuvant Therapy
for Breast Cancer (NCCTG
N9831/BCIRG006/BCIRG005)¹**

**Concordance of HER2 Central Assessment
by Two International Central Laboratories:
A Ring Study within the Framework of the
Adjuvant HER2-Positive ALTTO Trial
(BIG2-06/N063D/EGF106708)²**

¹Perez E et al.

Proc SABCS 2010;Abstract PD10-02.

²McCullough AE et al.

Proc SABCS 2010;Abstract P3-10-36.

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Round-Robin Review of HER2 Testing in the Context of Adjuvant Therapy for Breast Cancer (NCCTG N9831/BCIRG006/BCIRG005)

Perez E et al.

Proc SABCS 2010;Abstract PD10-02.

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Introduction

- HER2 is an important biomarker in the biology and treatment of breast cancer (BC), and reliable HER2 testing methodology is critical to BC care.
- Controversy exists regarding the definition of HER2 positivity (HER2+) and the type of test that may best predict the efficacy of anti-HER2 therapy.
- Interestingly, similar benefit of adjuvant trastuzumab has been observed in patients whose tumors were HER2+ by local laboratory and *either positive or normal* (negative) by central laboratory (*NEJM* 2008;358:1409; *JCO* 2010;28:4307).

Perez E et al. *Proc SABCS 2010;Abstract PD10-02.*

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Study Objectives

- **Primary objectives:**
 - Determine the concordance between HER2 results by three central laboratories (NCCTG, BCIRG and NSABP)
 - Determine the impact of round-robin review on discordant cases
 - Determine the intratumor heterogeneity of HER2 status
- **Secondary objective:**
 - Determine the impact of trastuzumab therapy for patients determined to have HER2-normal tumors after round-robin review

Perez E et al. *Proc SABCS 2010*;Abstract PD10-02.

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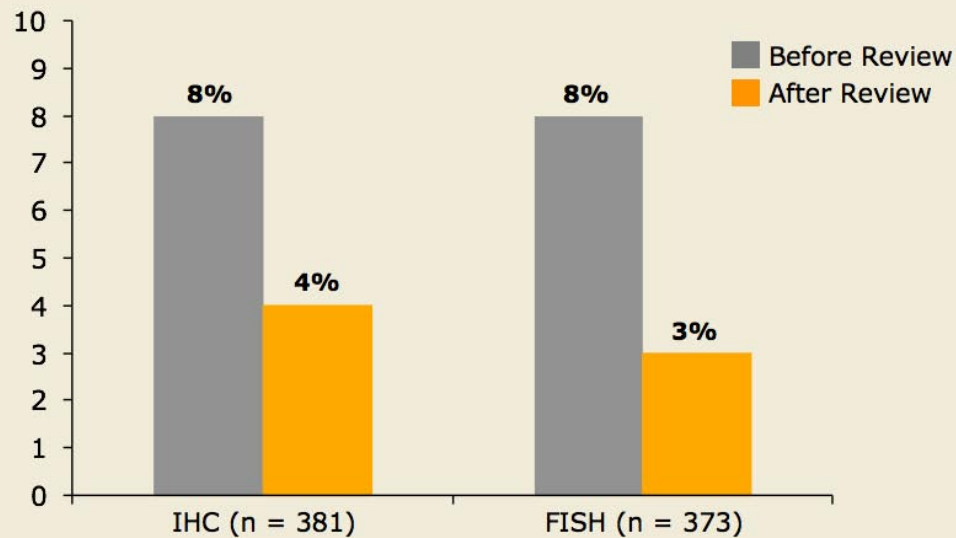
Materials and Methods

- **Materials**
 - Used specimens from three adjuvant trials (NCCTG N9831, BCIRG005, BCIRG006) for which HER2 testing for study enrollment was performed by both local and central labs:
 - Total number of IHC cases: 381
 - Total number of FISH cases: 373
- **Methods**
 - Blinded “round-robin” exchange of breast tumors among three central labs for confirmatory HER2 testing
 - FDA-approved definitions of HER2 positivity employed for both IHC and FISH testing
 - HER2 status independently determined at each central lab, and centrally discordant IHC and FISH cases were reviewed at a face-to-face meeting

Perez E et al. *Proc SABCS 2010*;Abstract PD10-02.

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HER2 Central Discordance Rates Pre- and Post-Round Robin Review



Adjudication led to reaching a consensus in 96% of IHC cases and in 97% of FISH cases

Perez E et al. *Proc SABCS 2010*;Abstract PD10-02.

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Author Conclusions

- Initial 8% discordance for each IHC and FISH among expert pathologists across three central laboratories was decreased to $\leq 4\%$ after round robin review.
- Excellent agreement ($\geq 96\%$) observed among the pathologists at review suggests that interpretation issues and tumor heterogeneity still play a role in discordant results.
- HER2 heterogeneity across blocks from the same tumor was observed more at the protein level than at the gene level (10% versus 5%, data not shown).
- Trastuzumab benefit was observed in the small subset of 53 N9831 patients **centrally** read as HER2-normal (although these were all initially read as HER2-positive **locally**, data not shown).
 - Disease-free survival HR = 0.34, $p = 0.06$

Perez E et al. *Proc SABCS 2010*;Abstract PD10-02.

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Concordance of HER2 Central Assessment by Two International Central Laboratories: A Ring Study within the Framework of the Adjuvant HER2-Positive ALTO Trial (BIG2-06/N063D/EGF106708)

McCullough AE et al.

Proc SABCS 2010;Abstract P3-10-36.

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Background

- Ongoing Phase III ALTO (**A**djuvant **L**apatinib and/or **T**rastuzumab **T**reatment **O**ptimization) trial for HER2+ BC
- Two central laboratories (European Institute of Oncology [IEO] and Mayo Clinic) confirming local HER2, ER and PR status prior to study entry
- Discordance between local and central laboratories identified:

Central Laboratory	HER2 % local false-positive	ER % discordant
IEO	14.5% of 8,037	12.1% of 9,021
Mayo Clinic	5.8% of 412	11.7% of 419

- **Current Study Goal:** Ring study to assess whether the central lab results of a subset of local/central discordant ALTO cases could be confirmed in the other central lab

McCullough AE et al. *Proc SABCS 2010;Abstract P3-10-36.*

Results and Author Conclusions

- 25 false-positive HER2 cases = **100% concordant** across central pathology review in HER2 IHC status (3+ vs 0-2+) and in HER2 FISH status (amplified vs not)
- 34 discordant ER cases = **85% concordant** across central pathology review when each used own IHC assay methodology
 - Increased to 100% concordance when a dual ER antibody cocktail utilized at both laboratories
- ALLTO enrollment ineligibility did not change when HER2 testing was performed by either IEO or Mayo Clinic central laboratories
- Standardized assays increase proficiency between laboratories (same test on same tissue = same result)

McCullough AE et al. *Proc SABCS 2010*;Abstract P3-10-36.

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Investigator Commentary: HER2 Testing in the Intergroup and ALTTO Adjuvant Trials

The study by Perez and colleagues was a follow-up to previously reported data from the NSABP, in which there was a suggestion that some patients with HER2-normal breast cancer may benefit from adjuvant trastuzumab. The investigators went back and evaluated the tissue samples from the Intergroup study and found a small percent of patients in whom there was discordance between IHC and FISH testing, even among experts. In almost every case they could find resolution to the issues causing discordance, but in the end there was still a small group of patients who appeared to have HER2-normal disease and benefited from trastuzumab. So in some troubling cases there is still a problem with HER2 testing, which is likely amplified in the community, with institutions doing fewer cases of HER2 testing than in larger referral centers.

In the BIG and NCCTG co-led ALTTO trial, expert pathologists from central laboratories were able to demonstrate 100 percent concordance for IHC and FISH testing of HER2 status, which suggests that using standardized tests and methodologies increases the likelihood of finding similar results.

Interview with William J Gradishar, MD, January 4, 2011

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