



Key SABCS Presentations
Issue 6, 2011

**The Use of Trastuzumab in the Elderly
in the Adjuvant Setting and
After Disease Progression
in Patients with HER2-Positive
Advanced 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 OBJECTIVES

- Counsel elderly patients with early HER2-positive breast cancer about the known benefits and risks of adjuvant trastuzumab in the population age 65 or older.
- Describe the emerging body of evidence for continued anti-HER2 treatment beyond disease progression for patients with HER2-positive breast cancer.

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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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The Use of Trastuzumab in the Elderly in the Adjuvant Setting and After Disease Progression in Patients with HER2-Positive Advanced Breast Cancer

Presentations discussed in this issue

Dall P et al. **Elderly patients in a prospective observation study on trastuzumab (Herceptin®) in the adjuvant treatment of breast cancer.** San Antonio Breast Cancer Symposium 2010; [Abstract P5-12-01](#).

Waddell T et al. **Trastuzumab beyond progression in HER2-positive advanced breast cancer: The Royal Marsden experience.** San Antonio Breast Cancer Symposium 2010; [Abstract P6-11-11](#).

Von Minckwitz G et al. **Final overall survival analysis of the TBP phase III study (GBG 26/BIG 3-05): Capecitabine vs capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment.** San Antonio Breast Cancer Symposium 2010; [Abstract P6-14-05](#).

Gruschkus SK et al. **Patterns of care and outcomes of HER2 positive metastatic breast cancer patients receiving 3rd line therapy in an outpatient community setting.** San Antonio Breast Cancer Symposium 2010; [Abstract P3-11-15](#).

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

The Use of Trastuzumab in the Elderly in the Adjuvant Setting and After Disease Progression in Patients with HER2-Positive Advanced Breast Cancer

Dall P et al.

Proc SABCS 2010;Abstract P5-12-01.

Waddell T et al.

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von Minckwitz G et al.

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Gruschkus SK et al.

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Elderly Patients in a Prospective Observation Study on Trastuzumab (Herceptin®) in the Adjuvant Treatment of Breast Cancer

Dall P et al.

Proc SABCS 2010;Abstract P5-12-01.

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Methods and Results (n=2,427)

Interim analysis of elderly patients from a prospective, observational German study of early breast cancer treated with adjuvant trastuzumab alone or in combination.

	<65 yrs (n=1,802)	≥65 yrs (n=625)	p-value
ECOG PS, 0	65%	52%	<0.0001
Chemotherapy	94%	90%	0.0025
Adjuvant chemotherapy	76%	82%	—
Neoadjuvant chemotherapy	18%	8%	<0.0001
Adjuvant endocrine therapy	56%	53%	—
Median LVEF*	64%	62%	0.037
Cardiac pathology*	6%	13%	<0.0001

*At the end of therapy

Dall P et al. *Proc SABCS 2010;Abstract P5-12-01.*

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Author Conclusions

- Trastuzumab is well tolerated and can be effectively used in patients with HER2-positive breast cancer without age restriction.
- Elderly patients with early HER2-positive breast cancer are more often treated with less aggressive treatment in combination with trastuzumab.
- Some differences were evident in cardiac safety and premature withdrawal from treatment among elderly patients treated with trastuzumab, but this did not affect disease-free survival (DFS) rates.
- The DFS rates after two and three years are 96% and 91%, respectively, and are in agreement with results of large randomized studies.
- Elderly patients with breast cancer appear to derive the same benefit from adjuvant trastuzumab treatment as younger patients.

Dall P et al. *Proc SABCS 2010*;Abstract P5-12-01.

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Trastuzumab Beyond Progression in HER2-Positive Advanced Breast Cancer: The Royal Marsden Experience

Waddell T et al.

Proc SABCS 2010;Abstract P6-11-11.

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Methods

- **Study design**
 - Retrospective, single-center study
- **Objective**
 - To evaluate the clinical efficacy and safety of continuing treatment with trastuzumab beyond progression and to compare those data to recently published literature.
- **Eligibility**
 - Metastatic or locally advanced HER-2 positive breast cancer (IHC3+ or FISH+)
 - Treated at Royal Marsden Hospital between January 2001 and December 2008
 - Continued receiving trastuzumab despite disease progression or relapsed within 12 weeks of completing adjuvant trastuzumab

Waddell T et al. *Proc SABCS 2010*;Abstract P6-11-11.

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Results

Outcome	Patients (%)
Radiological response	77 (68%)
Clinical response	16 (14%)
	Median (95% CI)
Time to progression	24 weeks (21-28 weeks)
Overall survival [†]	19 months (12-24 months)
Time to progression in subgroup*	25 weeks (18-33 weeks)
Overall survival in subgroup* [†]	22 months (17-27 months)

*Subgroup (n=81) selected to be comparable to German Study Group (*JCO* 2009;27:1999); [†]Measured from the continuation of trastuzumab at initial progression

Waddell T et al. *Proc SABCS 2010*;Abstract P6-11-11.

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Author Conclusions

- Continuing trastuzumab/HER2-directed therapy beyond disease progression had clinically meaningful benefit in this group of unselected patients.
- These data support the positive results and safety data from prior studies.

Waddell T et al. *Proc SABCS 2010*;Abstract P6-11-11.

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Final Overall Survival Analysis of the TBP Phase III Study (GBG 26/BIG 3-05): Capecitabine vs Capecitabine + Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer Progressing During Trastuzumab Treatment

von Minckwitz G et al.

Proc SABCS 2010;Abstract P6-14-05.

GBG 26/BIG 3-05 Study Design

Accrual: 156 (Closed)

Eligibility

HER2-positive
Locally advanced or metastatic breast cancer
Disease progression during treatment with trastuzumab



X, d1-14 q3wk

X d1-14 q3wk plus H q3wk (XH)

X=capecitabine 2,500 mg/m²
 H=trastuzumab 6 mg/kg

*Patients were stratified according to previous therapy

Primary objective: Time to progression

Secondary objectives: Overall response rate, duration of response, clinical benefit and overall survival

von Minckwitz G et al. *Proc SABCS 2010*;Abstract P6-14-05.

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Results

	X (n=74)	XH (n=77)	p-value
Overall survival (OS)	20.6 mos	24.9 mos	0.73
	X (n=53)	XH (n=31)	p-value
OS in patients without crossover	20.4 mos	26.7 mos	0.2
	X (n=88)	XH (n=52)	p-value
OS in the 3 rd -line setting (includes crossovers)	13.3 mos	18.8 mos	0.02

von Minckwitz G et al. *Proc SABCS 2010*;Abstract P6-14-05.

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Author Conclusions

- Final OS analysis of the GBG 26/BIG 3-05 study could not demonstrate a statistically significant survival benefit for treatment beyond progression with trastuzumab.
 - OS=20.6 vs 24.9 months ($p=0.73$)
- A post-hoc analysis of patients receiving trastuzumab in the 3rd-line setting reported an improved OS compared to those who did not continue with trastuzumab therapy.
 - OS=13.3 vs 18.8 months ($p=0.02$).
- Overall it seems important for patients with HER2-positive breast cancer to continue anti-HER2 treatment despite disease progression.

von Minckwitz G et al. *Proc SABCS 2010*;Abstract P6-14-05.

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Patterns of Care and Outcomes of HER2-Positive Metastatic Breast Cancer Patients Receiving 3rd Line Therapy in an Outpatient Community Setting

Gruschus SK et al.

Proc SABCS 2010;Abstract P3-11-15.

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Methods and Results N=139 (from Abstract)

Retrospective study of data from US Oncology's iKnowMed record system of patients with HER2+ metastatic breast cancer treated with 1st-line trastuzumab between 1/1/2006 and 7/31/2007 to identify outcomes and patterns of care in patients receiving 3rd-line treatments.

	1st-line therapy n=139	2nd-line therapy n=139	3rd-line therapy n=48
Progressive disease during follow-up period	66% (n=92)	35% (n=48)	56% (n=27)
Median time to progression from 1 st - to 3 rd -line therapy (95% CI)	35 months (30.7-39.3 months)		
Deaths prior to progression to 3 rd line (n)	17% (23)		
Patients alive without progression to 3 rd -line therapy at end of follow-up (n)	49% (68)		

Gruschkus SK et al. *Proc SABCs 2010*;Abstract P3-11-15.

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Author Conclusions

- In this retrospective analysis, 35% of patients received 3rd-line therapy and 49% were alive without progression to the 3rd line during the observation period.
- Utilization of 3rd- and 4th-line therapy varied widely (data not shown).
 - Suggests a standard of care has not emerged in this community-based setting.
- Continued active therapy past the 3rd line appears common in this setting. However, its usefulness may decrease in the 4th-line setting (data not shown).

Gruschkus SK et al. *Proc SABCs 2010*;Abstract P3-11-15.

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Investigator Commentary: Trastuzumab in the Elderly; Treatment After Disease Progression

In this European registry study of patients with HER2-positive early breast cancer, there did not appear to be a significant difference between older and younger patients in terms of the benefits derived from adjuvant trastuzumab, which has been seen in other studies also. The investigators observed a small but limited increase in cardiac issues, which may be the result of the older age group of patients and other comorbidities.

In the poster by Waddell and colleagues, they report on the Royal Marsden single-institution study, which appeared to corroborate the von Minckwitz German group data that suggested a benefit for continuing trastuzumab beyond disease progression for patients with HER2-positive advanced breast cancer.

In previous reports, von Minckwitz demonstrated an improvement in progression-free survival with the continuation of trastuzumab beyond disease progression. In this final analysis, no improvement in overall survival was demonstrated. In the subset of patients who received anti-HER2 therapy in the 3rd-line setting a survival benefit was observed, but that was a subset analysis in a small number of patients.

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

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