5 Minute JournalClub

Key SABCS Presentations

Issue 6, 2011

Efficacy of HER2-Based Therapy in Patients After Failure of Prior T-DM1 Therapy and the Evaluation of an Anti-HER2 Combination Regimen

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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

- Explain the preliminary efficacy and safety of dual HER2-directed treatment with pertuzumab and trastuzumab-DM1 in patients with advanced breast cancer.
- Recall the benefits of using HER2-directed therapy as subsequent treatment for patients who experienced disease progression on prior trastuzumab-DM1.

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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.

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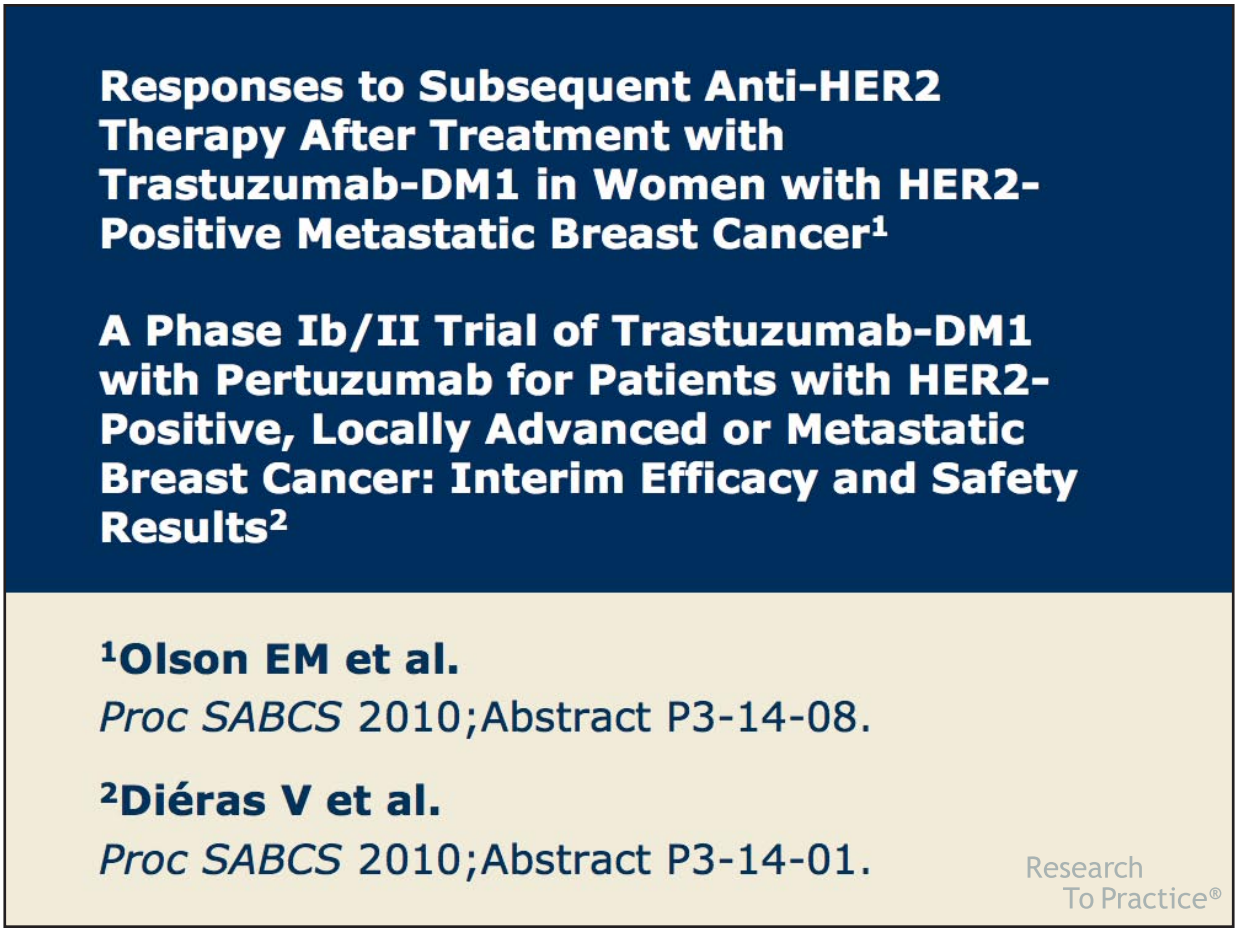
Efficacy of HER2-Based Therapy in Patients After Failure of Prior T-DM1 Therapy and the Evaluation of an Anti-HER2 Combination Regimen

Presentations discussed in this issue

Olson EM et al. **Responses to subsequent anti-HER2 therapy after treatment with trastuzumab-DM1 in women with HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract P3-14-08**.

Diéras V et al. **A phase Ib/II trial of trastuzumab-DM1 with pertuzumab for patients with HER2-positive, locally advanced or metastatic breast cancer: Interim efficacy and safety results.** San Antonio Breast Cancer Symposium 2010;**Abstract P3-14-01**.

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



Responses to Subsequent Anti-HER2 Therapy After Treatment with Trastuzumab-DM1 in Women with HER2-Positive Metastatic Breast Cancer

Olson EM et al.

Proc SABCS 2010;Abstract P3-14-08.

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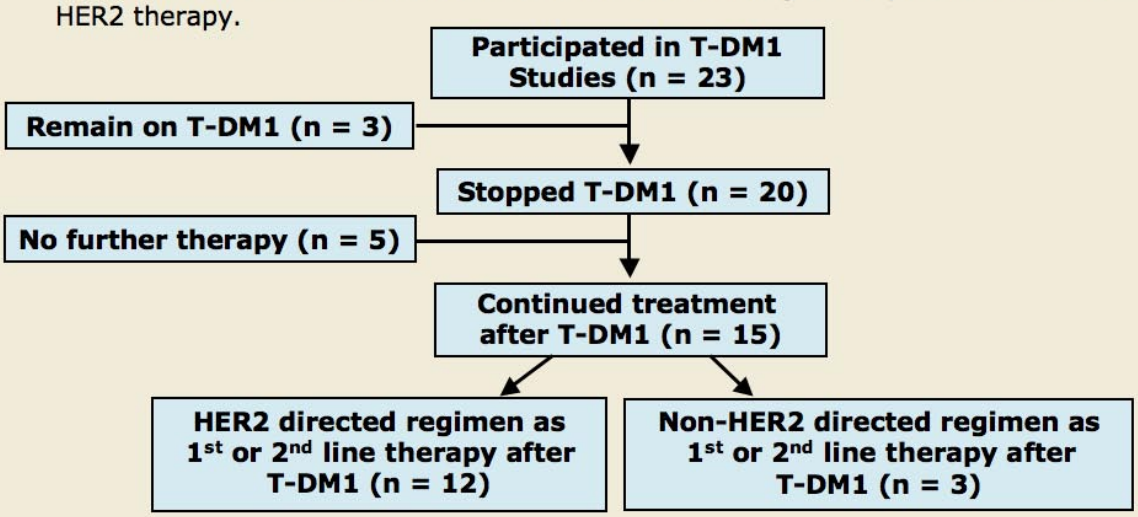
Study Objective and Participant Flow

Primary objective: Retrospective, single-institution study of women with progressive disease following treatment with trastuzumab-DM1 (T-DM1) during clinical trials, conducted to determine outcomes following subsequent lines of anti-HER2 therapy.



Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

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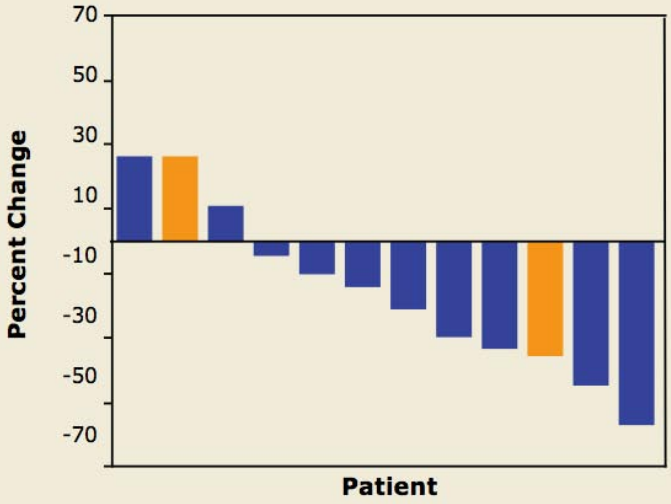
Decreases in Target Lesions



Best response to 1st or 2nd line of subsequent therapy after treatment with T-DM1. Blue bars indicate patients treated with trastuzumab and/or lapatinib-based regimens; orange bars indicate patients treated with non-trastuzumab and non-lapatinib based regimens only.

With permission from Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08. Research To Practice®

Overall Response

HER2 directed regimen as 1st or 2nd line therapy after T-DM1 (n = 12)

↓

Partial response, 33% (n = 4)

↓

Median duration of therapy to 1st HER2 regimen after T-DM1: 5.5 months

Received a 2nd regimen after T-DM1 (n = 9)

↓

Median duration of therapy to 2nd HER2 regimen after T-DM1: 6.4 months

Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

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Author Conclusions

- Prior exposure to T-DM1 does not exhaust the potential benefit of ongoing anti-HER2 therapy with trastuzumab- and/or lapatinib-based regimens in patients with heavily pretreated HER2-positive metastatic breast cancer.
- This is the first report of outcomes to subsequent treatment after T-DM1.

Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

A Phase Ib/II Trial of Trastuzumab-DM1 with Pertuzumab for Patients with HER2-Positive, Locally Advanced or Metastatic Breast Cancer: Interim Efficacy and Safety Results

Diéras V et al.

Proc SABCS 2010;Abstract P3-14-01.

Background

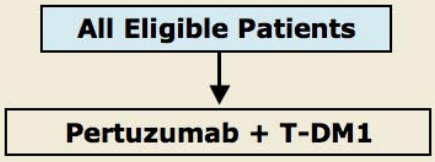
- Trastuzumab-DM1 (T-DM1) contains the cytotoxic maytansine derivative DM1 coupled to trastuzumab using a unique and stable linker.
- The linker allows for the intracellular release of DM1 after trastuzumab binds to HER2-overexpressing tumor cells; therefore, systemic exposure to free DM1 is minimized.
- Pertuzumab is the first HER2-directed dimerization inhibitor for the treatment of metastatic breast cancer (mBC).
- In xenograft models, the combination of T-DM1 and pertuzumab has shown synergistic activity.
- **Objective**
  - To evaluate the safety, tolerability and objective response rates of T-DM1 plus pertuzumab.

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

TDM4373g Study Design

Accrual: 67 (Closed)

Eligibility
Locally advanced or metastatic breast cancer
HER2-positive
Prior treatment with trastuzumab
No prior treatment with T-DM1 or pertuzumab
LVEF ≥55%



Pertuzumab: 840 mg X 1 → 420 mg in subsequent cycles, q3wk
T-DM1: 3.6 mg/kg, q3wk

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Objective Responses among Patients in 1st-Line and Relapsed Settings

Clinical outcome	1st-line (n = 21)	Relapsed (n = 46)
Confirmed objective response rate	57.1%	34.8%
Clinical benefit rate*	61.9%	45.7%
Best responses		
Complete response	9.5%	2.2%
Partial response	47.6%	32.6%
Stable disease	23.8%	47.8%
Progressive disease	19.0%	15.2%

* Objective response or maintenance of stable disease for at least 6 months from start of study treatment

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

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Select Grade ≥3 Adverse Events*

Adverse event (AE)	(n = 67)†
Fatigue	11.9%
Thrombocytopenia	11.9%
Alanine aminotransferase increased	9.0%
Aspartate aminotransferase increased	7.5%
Cellulitis	6.0%
Dyspnea	6.0%
Anemia	4.5%
Pleural effusion	4.5%
Pneumonia	3.0%
Neutropenia	3.0%

* Grade ≥3 AEs occurring in more than one patient. Data reflect number of patients, not number of events; some patients experienced an AE at more than one grade.

† Includes one Grade 5 pneumonia event and four Grade 4 events (three thrombocytopenia and one pain).

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

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Safety

- The Phase Ib portion of this study reported that it was safe to combine full doses of T-DM1 and pertuzumab.
- Serious adverse events
  - Pleural effusion (n = 3 - relapsed, 0 - 1st line)
  - Dyspnea (n = 2 - relapsed, 1 - 1st line)
  - Pneumonia (n = 2 - relapsed, 0 - 1st line)
  - Abdominal pain (n = 0 - relapsed, 2 - 1st line)
  - Vomiting (n = 1 - relapsed, 1 - 1st line)
  - Cellulitis (n = 2 - relapsed, 0 - 1st line)
- Grade 5 pneumonia in a relapsed patient who subsequently died due to disease progression.
- No relapsed patients and one 1st-line patient experienced a left ventricular ejection fraction (LVEF) decline of ≥25% from baseline value.
- One relapsed patient discontinued from the study due to Grade 3 LVEF dysfunction.

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

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Author Conclusions

- T-DM1 and pertuzumab were well tolerated at full single-agent doses as used in other clinical studies.
- The combination of T-DM1 and pertuzumab provides encouraging efficacy in patients with mBC:
  - Confirmed ORR in 1st-line setting = 57.1%
    - Robust activity reported for patients who received prior trastuzumab and taxane therapy in the early breast cancer setting (data not shown)
  - Confirmed ORR in relapsed setting = 34.8%
- The combination of T-DM1 and pertuzumab has an acceptable safety and tolerability profile.
- The combination of T-DM1 and pertuzumab is being studied as 1st-line treatment for HER2-positive mBC in the ongoing Phase III MARIANNE trial (BO22589/TDM4788g):
  - Randomization: T-DM1 alone or in combination with pertuzumab versus trastuzumab plus taxane

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

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Investigator Commentary: Early Experience with T-DM1

The report by Diéras and colleagues was of a Phase I/II study, so we don't yet have all of the results, but the study clearly demonstrated activity with the combination of trastuzumab-DM1 (T-DM1) and pertuzumab for patients with advanced HER2-positive breast cancer in the 1st-line or relapsed settings, and no significant toxicity was associated with this anti-HER2 combination. This study supports the idea of using anti-HER2 agents that have different mechanisms of action together.

The issue addressed in the study by Olson and colleagues is analogous to the situation with certain hormonal therapies. For instance, when we administer fulvestrant and downregulate the estrogen receptor, we worry about being able to induce a response with other endocrine therapies. In this small study, the investigators demonstrated that some patients with HER2-positive metastatic breast cancer whose disease progressed on T-DM1 would respond to subsequent anti-HER2 therapy with trastuzumab or lapatinib. So treatment with T-DM1 does not preclude future benefit from other anti-HER2 therapies.

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