



**Phase II Study of Trastuzumab-
DM1 (T-DM1) for Patients with
Previously Treated HER2-Positive
Metastatic Breast Cancer**

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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

- Assess the efficacy of the anti-HER2 agent T-DM1 in the treatment of patients with HER2-positive metastatic breast cancer who have experienced disease progression on chemotherapy and anti-HER2 therapy.

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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:

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IN THIS ISSUE:

The long awaited and maybe not so satisfying [third analysis of BCIRG trial 006](#) (TCH versus AC->TH versus AC->T)

- [NCCTG trial 9831](#) data again suggests an advantage to combining chemotherapy and trastuzumab as opposed to sequencing
- Another happy chapter in the rapidly evolving [T-DM1 story](#) with more data demonstrating surprising efficacy in far advanced disease

As Dennis Slamon concluded his [BCIRG 006 presentation](#) in San Antonio last month, I wondered if years from now that moment would symbolize in my mind the end of interest in clinical research on cytotoxic chemotherapy. A generation or more of oncologists have seen the promise and disappointment of these difficult agents, and trials like 006 have sparked endless discussion about which chemo is optimal, a topic that used to permeate all of oncology clinical research.

Since presenting the first “TCH” data set at the 2005 San Antonio meeting, Dr Slamon and others have debated the merits and downsides of anthracyclines in patients with HER2-positive tumors, and a corollary chemo presentation in San Antonio by Dr Edith Perez of [NCCTG trial 9831](#) provided more evidence of the value of combining cytotoxics and trastuzumab as opposed to sequencing with chemo followed by T à la the HERA trial.

The question is: “Who cares anymore?”

In a commentary that accompanies our slide sets this week, Dr Mark Pegram makes the compelling argument that it’s pretty much time to move on from these Talmudic debates on the unknowable, like whether TCH is a better option than AC->TH, and perhaps focus more energy on enrolling patients in studies of new anti-HER2 therapies, like the pretty unusual [T-DM1](#) molecule, which once again in San Antonio put forth unprecedented efficacy numbers in patients with multiple prior anti-HER2 treatments. One might argue that the tiny dollop of maytansine delivered by trastuzumab in T-DM1 is in fact chemotherapy but without alopecia, GI toxicity and myelosuppression.

Everyone in oncology, along with thousands of anxious women who have received adjuvant therapy for HER2-positive breast cancer, have their fingers crossed that we can quickly assess the optimal role of T-DM1 — and for that matter the antibody

pertuzumab and TKIs like lapatinib and neratinib — and have available a new level of treatment efficacy. Hopefully research advances will accelerate in a similar manner for the other 80 percent of patients with HER2-negative tumors.

Next up on 5-Minute Journal Club: “Practice-changing” data on the estrogen receptor downregulator fulvestrant.

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Phase II Study of Trastuzumab-DM1 (T-DM1) for Patients with Previously Treated HER2-Positive Metastatic Breast Cancer

Presentation discussed in this issue

Krop I et al. **A Phase II study of trastuzumab-DM1 (T-DM1), a novel HER2 antibody-drug conjugate, in patients previously treated with lapatinib, trastuzumab, and chemotherapy.** SABCS 2009; [Abstract 5090](#).

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

A Phase II Study of Trastuzumab-DM1 (T-DM1), a Novel HER2 Antibody-Drug conjugate, in Patients with HER2+ Metastatic Breast Cancer who were Previously Treated with an Anthracycline, a Taxane, Capecitabine, Lapatinib and Trastuzumab

Krop I et al.
SABCS 2009;Abstract 5090.

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Introduction

- T-DM1 combines the HER2 targeting function of trastuzumab (T) with the DM1 anti-microtubule derivative.
- Proof-of-concept phase II study (4258g) examined single-agent T-DM1 in patients with previously treated, HER2+, metastatic breast cancer (*JCO* 2009;27;Abstract 1017).
 - In patients previously treated with lapatinib and T:
 - Objective response rate (ORR)=24.2%
 - In patients that were retrospectively, centrally confirmed HER2+:
 - ORR=33.8%
 - T-DM1 was well tolerated at the study dose and schedule (3.6 mg/kg IV q3wk).
- **Current study objectives:**
 - Confirm and extend findings of 4258g study in a homogenous population of patients with HER2+ metastatic breast cancer (mBC) that had been previously treated with chemotherapy, lapatinib and T.

Source: Krop I et al. SABCS 2009;Abstract 5090.

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4374g: Phase II, Open-Label, Multicenter Trial of T-DM1 in Previously Treated Patients with mBC

Eligibility (n=110)

Progressive, HER2+ disease (FISH+ or IHC 3+)

Prior treatment with anthracycline, taxane, capecitabine, lapatinib or T

At least two anti-HER2 regimens in the metastatic setting

No prior history of significant cardiac disease

No untreated or symptomatic brain metastases within 2 months of first dose

T-DM1
3.6 mg/kg IV q3wk

Source: Krop I et al. SABCS 2009;Abstract 5090.

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Prior Chemotherapy and Anti-HER2 Therapy

	n=110
Median number of agents for metastatic disease (range)*	7.0 (1 - 15)
Median number of agents in all therapy settings (range)*	8.0 (1 - 19)
Number of patients with 5 prior agents (%)**	109 (99.1)
Median duration of prior T in metastatic setting (range)	19.4 mos (2 - 116)
Median duration of prior lapatinib in metastatic setting (range)	6.9 mos (0 - 23)

*Includes all agents intended for the treatment of breast cancer except hormonal therapy.

**One patient did not receive a taxane.

Source: Krop I et al. SABCS 2009;Abstract 5090.

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T-DM1 Exposure

	n=110
Number of doses administered, median (range)	7.0 (1 - 19)
Exposure duration, median (range)	19.3 weeks (0 - 56)
Average T-DM1 dose, median (range)	3.57 mg/kg (2.5 - 3.9)
Dose reductions*	
Patients with dose reductions to 3.0 mg/kg	11
Patients with dose reductions to 2.4 mg/kg	6

*Values reported are from an independent review facility assessment.

Source: Krop I et al. SABCS 2009;Abstract 5090.

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Efficacy Results (median follow-up 8.3 mos)

Clinical Response*	All Treated Patients (n=110)	HER2+ Patients ¹ (n=76)	HER2 Normal Patients ¹ (n=15)
ORR	32.7%	39.5%	20.0%
Complete response	0%	—	—
Partial response	32.7%	—	—
Clinical benefit rate (CBR)	44.5%	52.6%	26.7%

*Values reported are from an independent review facility assessment.

¹HER2 status was retrospectively centrally confirmed.

Source: Krop I et al. SABCS 2009;Abstract 5090.

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Serious Adverse Events Occurring in ≥2 Patients

Adverse Event (All Grades)	n=110
Pyrexia	2.7%
Cellulitis	2.7%
Pneumonia	2.7%
Nausea	1.8%
Axillary pain	1.8%
Convulsion	1.8%
LVEF*	
Post-baseline < 45%	0%
Maximum decrease from baseline ≥ 25%	0%

*n=107

Source: Krop I et al. SABCS 2009;Abstract 5090.

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Conclusions

- T-DM1 demonstrated anti-tumor activity in an extensively pretreated population of patients with mBC.
 - ORR=32.7% and CBR=44.5%
- Clinical benefit was observed in a prespecified patient population not previously studied.
 - Patients having received prior treatment with an anthracycline, a taxane, capecitabine, lapatinib and T
 - Patients having received two HER2-directed regimens in the metastatic setting
 - Patients with progressive disease on last regimen received
- T-DM1 was well tolerated with no observed dose-limiting cardiotoxicity or new safety signals.

Source: Krop I et al. SABCS 2009;Abstract 5090.

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DR PEGRAM: Trastuzumab-DM1 (T-DM1) is an immunoconjugate with trastuzumab as the backbone. The idea is to use trastuzumab as a vehicle to deliver a microtubule-interacting poison, maytansine, which as a single agent is too toxic to be given to humans via IV. But when it's coupled to trastuzumab, it's really a potent cytotoxic against HER2-positive tumor target cells.

I found amazing the high degree to which the patient population had been pretreated in this study. Given such a heavily pretreated patient population, you might expect that there would be no efficacy signal for a new targeted agent in that setting. But single-agent T-DM1 demonstrated a response rate of 39.5 percent in that patient population with HER2-positive disease.

I think that it is stunning to have a patient population treated previously with lapatinib, trastuzumab and chemotherapy and to still retain an efficacy signal greater than a third. There have been previous papers showing that T-DM1 really requires HER2 overexpression for activity. There should be a low expectation for collateral damage to other normal tissues that lack HER2 overexpression compared to the HER2-positive tumor targets. Also T-DM1 does not cause alopecia, neutropenia or extensive nausea/vomiting. This begs the question in my mind: Can T-DM1 replace chemotherapy in combination with trastuzumab? I think that's an extremely intriguing question and one that absolutely merits the attention of clinical trialists and the cooperative groups.

DR LOVE: Are there trials up and running that are looking at T-DM1 versus chemotherapy/trastuzumab?

DR PEGRAM: The current ongoing registration trial is a Phase III trial of T-DM1 as a single agent versus capecitabine with lapatinib in a patient population that would be suitable for capecitabine with lapatinib treatment. If that study is positive, then the next move that I would like to see would be a head-on comparison of T-DM1 versus trastuzumab/chemotherapy. I've seen a Phase II study underway evaluating the efficacy and safety of taxane/trastuzumab versus T-DM1 in patients who have not received prior chemotherapy for metastatic disease. Neoadjuvant trials looking at T-DM1 head on against chemotherapy/trastuzumab would also be an ideal study design to critically interrogate its capabilities.

DR LOVE: Do you think we're moving fast enough in studying T-DM1?

DR PEGRAM: The process of meeting the regulatory requirements, though necessary, is painstaking and slow. When you see something this potent, your immediate instinct is to want to move it forward as quickly as possible. I think it is being moved forward as quickly as possible — the registration trial is already underway. Once it gets a label indication, it will allow for numerous investigator-initiated trials and will automatically spark an interest on the part of the cooperative groups to do adjuvant studies.

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