5 Minute JournalClub

Key ASCO Presentations
Issue 5, 2010

Combination Anti-HER2 Therapy with Pertuzumab for Patients with HER2-Positive Metastatic Breast Cancer (mBC) Previously Treated with Trastuzumab

For more visit ResearchToPractice.com/5MJCMT2010

Research To Practice®

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 tens of thousands of 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 OBJECTIVES

- Recall the safety and early clinical activity of pertuzumab with T-DM1 in patients with HER2-positive mBC.
- Describe potential prognostic and/or predictive biomarkers for patients with HER2-positive mBC treated with pertuzumab and trastuzumab.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides. To receive credit, the participant should review the slide presentation and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Kathy D Miller, MD
Sheila D Ward Scholar of Medicine
Associate Professor of Medicine
The Indiana University Melvin and Bren Simon Cancer Center
Indianapolis, Indiana

Advisory Committee: Genentech BioOncology, MethylGene Inc, Roche Laboratories Inc; Speakers Bureau: Genentech BioOncology, Roche Laboratories Inc.

Eric P Winer, MD
Thompson Investigator in Breast Cancer Research
Chief, Division of Women's Cancers
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

No real or apparent conflicts of interest to disclose.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, Lilly USA LLC, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Spectrum Pharmaceuticals Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

Last review date: July 2010
Expiration date: July 2011

5 MinuteJournalClub

Key ASCO Presentations
Issue 5, 2010

To go directly to the slides and commentary, **click here**.

The oral sessions on breast cancer in Chicago this year reflected a huge volume of ongoing research, and as usual there were lots of important messages for oncologists in practice, including the following:

1. **Axillary node dissection is on the way out, while intraoperative breast irradiation may be on the way in**
   Several related trial reports were the highlight of one major oral session. The NSABP confirmed what most have believed for years: There is no value in axillary dissection for a patient with a clinically negative axilla and a well-performed negative sentinel node biopsy. Two American College of Surgeons trials demonstrated no prognostic value in IHC staining of H&E-negative sentinel nodes and showed that axillary dissection may not be necessary in all patients with positive sentinel nodes. Finally, the legendary trial champion Mike Baum **proved that** 30 minutes of intraoperative radiation therapy with a $300,000 device may yield comparable results to six weeks of conventional radiation therapy in patients after lumpectomy.

2. **Anti-HER2 therapy continues to gallop along**
   Kathy Miller's early data evaluating the fascinating combination of the chemo/trastuzumab conjugate T-DM1 plus the novel anti-HER2 dimerization inhibitor pertuzumab demonstrated safety, and a related study revealed some possible tissue correlates with efficacy. It's challenging to think of a more creative systemic strategy presented at ASCO.

3. **More of the same and something new for advanced disease**
   Two presentations on bevacizumab/chemotherapy reinforced much of what we already knew. The first, Joyce O'Shaughnessy's presentation of a mini-meta-analysis of first-line bev/chemo trials confirmed the benefit of this agent on progression-free but not overall survival. This seems to be an emerging theme in cancers with long natural histories, as first-line trials often fail to show a survival benefit, whereas studies with patients who have received multiple prior treatments may show a survival advantage, perhaps because of the complexities of post-first-line therapy, including the potential for crossover. Chris Twelves' ASCO data set

demonstrating a survival advantage with the **new antitubulin agent eribulin** is a clear example of this increasingly discussed phenomenon.

In a second presentation addressing anti-angiogenic therapy for advanced breast cancer, Adam Brufsky's reanalysis of the second-line RIBBON 2 trial demonstrated what most believed already: The impact of bev seems relatively independent of its chemo partner.

Next up on 5-Minute Journal Club: The once-mighty imatinib gets another shove out the door with new data on dasatinib, nilotinib and bosutinib in CML.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the five educational activities, comprised of a slide set, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

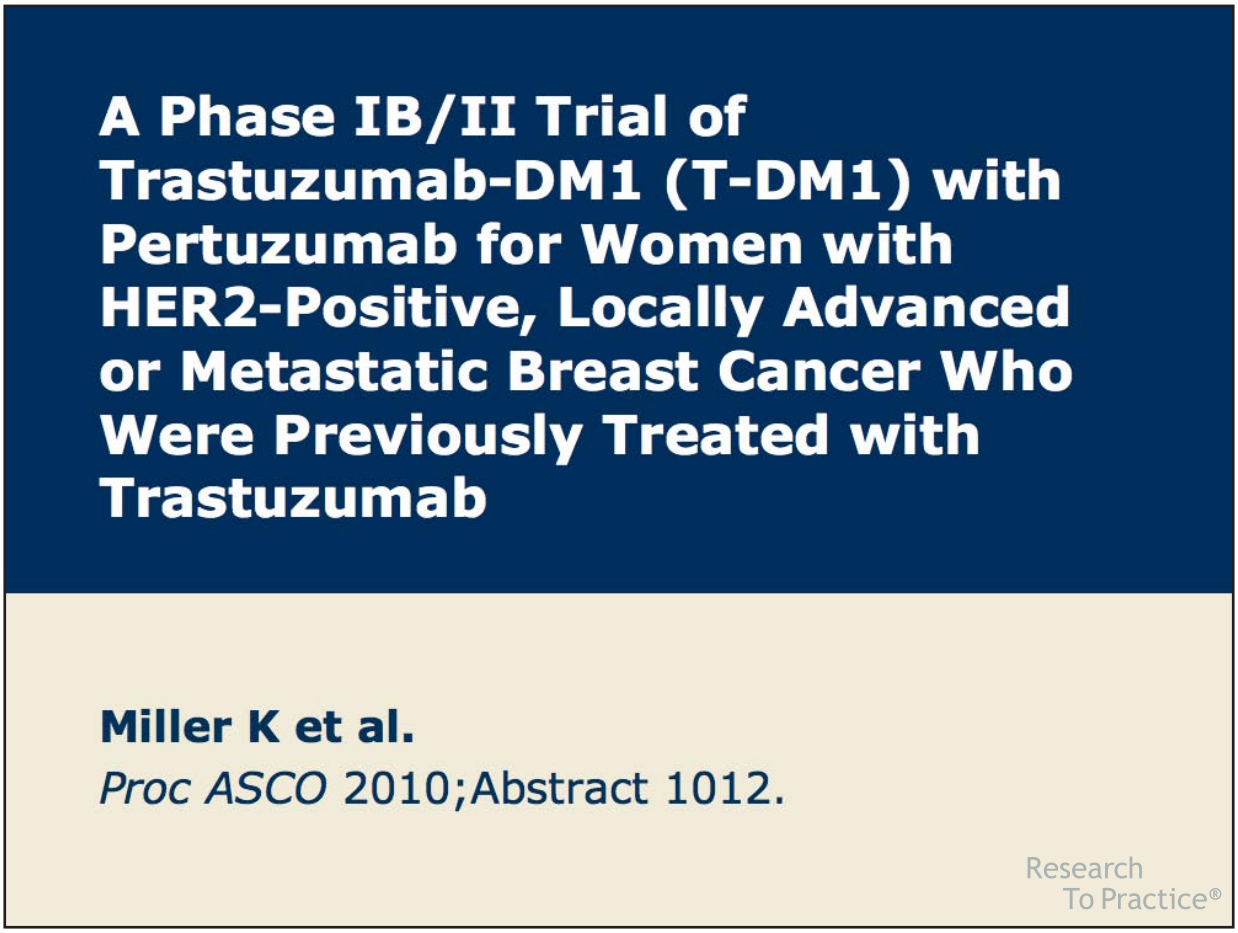
Combination Anti-HER2 Therapy with Pertuzumab for Patients with HER2-Positive Metastatic Breast Cancer (mBC) Previously Treated with Trastuzumab

Presentations discussed in this issue

Miller K et al. **A phase Ib/II trial of trastuzumab-DM1 (T-DM1) with pertuzumab for women with HER2-positive, locally advanced or metastatic breast cancer who were previously treated with trastuzumab.** *Proc ASCO* 2010;**Abstract 1012**.

Cortes J et al. **Pertuzumab and trastuzumab: Exploratory biomarker correlations with clinical benefit in patients with metastatic HER2-positive breast cancer.** *Proc ASCO* 2010;**Abstract 1066**.

Slides from presentations at ASCO 2010 and transcribed comments from recent interviews with Kathy D Miller, MD (6/11/10) and Eric P Winer, MD (7/6/10)



Introduction

- Phase II trials have shown that T-DM1, a HER2-targeted antibody-drug conjugate, has encouraging single-agent activity in heavily pretreated patients with HER2-positive metastatic breast cancer.
- Pertuzumab is a HER2-targeted monoclonal antibody that inhibits HER2 dimerization with other members of the HER2 receptor family.
- **Current study objective:**
  - Assess the safety and efficacy of T-DM1 and pertuzumab combination therapy in patients with HER2-positive locally advanced or metastatic breast cancer.
  - Preliminary efficacy and safety results are presented only for relapsed patients evaluable as of December 14, 2009.

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

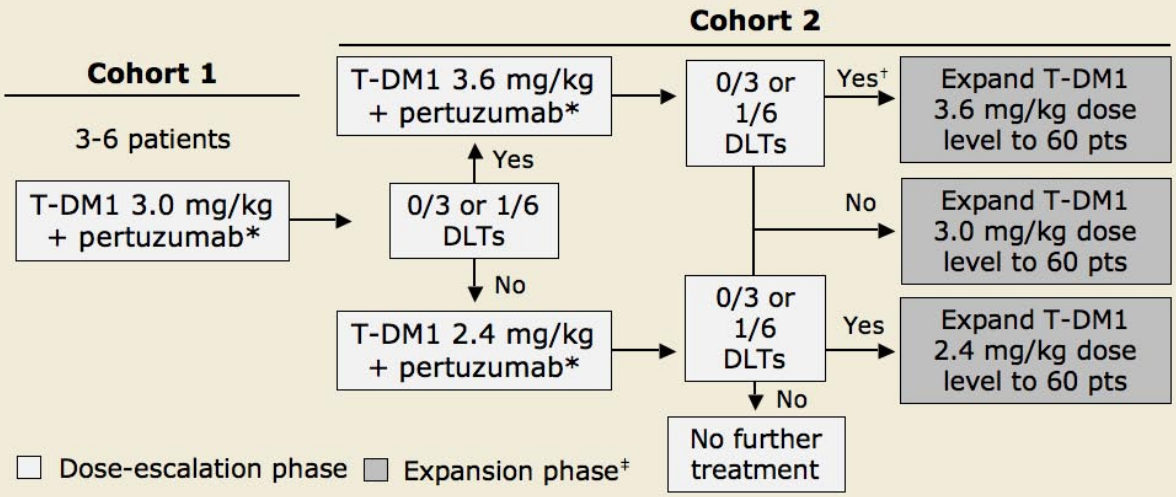
Study Design

- Key inclusion criteria:
  - Measurable disease with histologically confirmed locally advanced or metastatic HER2-positive breast cancer
    - FISH+ or CISH+ or IHC3+
  - No prior T-DM1 or pertuzumab therapy
  - Prior HER2 therapy in the second-line or beyond setting
  - Cardiac ejection fraction >55%
- In this 3 + 3 design, patients (N = 9) received pertuzumab (840 mg, cycle 1; 420 mg, cycle 2 and beyond) with T-DM1 (3.0 mg/kg in Cohort 1 and, in the absence of dose-limiting toxicity (DLT), 3.6 mg/kg in Cohort 2).
- Additional patients were added to the expansion phase (N = 58) after the dose escalation phase was completed.

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

Trial Schema



* Full-dose pertuzumab, cycle 1 loading dose (840 mg, 420 mg all subsequent cycles)
† Patients enrolled in initial cohort may now receive 3.6 mg/kg T-DM1 in subsequent cycles along with full-dose pertuzumab
‡ 20 first-line and 40 relapsed patients were to be included in this phase

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

Response in Relapsed Patients

	Cohort 1 (n = 3)	Cohort 2 (n = 25)	Total (n = 28)
Complete response	0	0	0
Partial response	66.7%	32.0%	35.7%
Stable disease	33.3%	48.0%	46.4%
Progressive disease	0	16.0%	14.3%
Missing	0	4.0%	3.6%

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

Safety

- Dose reductions due to AEs in 6 patients:
  - Hematologic events (n = 3), nausea/vomiting (n = 1) and increased liver enzymes (n = 2)
- Serious AEs were observed in 7 patients:
  - Grades 3 and 5 pneumonia (n = 2), Grade 3 nausea/diarrhea/fatigue/vomiting (n = 1), Grade 3 cellulitis (n = 1), dyspnea (n = 1), hematuria (n = 1) and URI (n = 1)
- One discontinuation of both drugs (Grade 3 LV dysfunction)
- One death occurred unrelated to treatment (Grade 5 pneumonia in patient who died concomitantly of disease progression)

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

Grade 3/4 Adverse Events

Event	Patients, %
Fatigue	13.6%
Thrombocytopenia	11.3%
AST increase	6.8%
Nausea	4.5%
Vomiting	4.5%
Diarrhea	2.3%
Dyspnea	2.3%

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Research To Practice®

Conclusions

- The dose of T-DM1 was determined to be 3.6 mg/kg in combination with full-dose pertuzumab (840 mg loading dose followed by 420 mg).
- T-DM1 plus full-dose pertuzumab has an encouraging safety and tolerability profile.
- The preliminary efficacy data of T-DM1 plus pertuzumab for relapsed patients are encouraging.
  - Overall response rate was 35.7%.
  - All responses were confirmed partial responses.

Miller K et al. *Proc ASCO* 2010;Abstract 1012.

Investigator comment on the results of a Phase Ib/II trial of T-DM1 with pertuzumab for patients with advanced HER2-positive BC treated with trastuzumab

In the Phase I dose-escalation cohort of this study, we observed no obvious increase in toxicity, and we were able to escalate doses of both T-DM1 and pertuzumab to what we considered standard Phase II doses. The trial then expanded into two Phase II cohorts — patients refractory to trastuzumab and a smaller first-line therapy cohort of patients who received neoadjuvant or adjuvant trastuzumab but had not received trastuzumab for mBC. We did not present data for this first-line therapy cohort but reported on the first 28 out of 44 patients in the refractory cohort.

The toxicities with the combination appear similar to what would be expected from T-DM1 alone, including mild fatigue and some thrombocytopenia, which was not clinically significant. No obvious cardiotoxicity was observed, although all of these patients had previously received trastuzumab and most had received lapatinib as well. Response rates were between 25 to 30 percent in this refractory population. We were certainly encouraged by these results and by the apparent lack of increased toxicity.

Interview with Kathy D Miller, MD, June 11, 2010

Investigator comment on the results of a Phase Ib/II trial of T-DM1 with pertuzumab for patients with advanced HER2-positive BC treated with trastuzumab

T-DM1 is an antibody-drug conjugate, or trastuzumab linked to a small amount of the chemotherapeutic agent maytansinoid. With T-DM1, the trastuzumab moiety binds to the HER2-positive cancer cell, the molecule is internalized and the chemotherapy is released in a targeted fashion.

Two prior Phase II studies with T-DM1 demonstrated that it was quite effective, based on response rates of approximately 35 percent in patients with highly refractory, HER2-positive mBC. Pertuzumab is another monoclonal antibody that binds to a different site on HER2 and prevents heterodimerization of HER2 with either HER1 or HER3.

In Kathy's study, they demonstrated that T-DM1 and pertuzumab could safely be administered together. It's difficult to comment on efficacy in this small study, although response rates with the combination were similar to what has been observed with T-DM1 alone. This does not mean that this combination will not be more effective than T-DM1, particularly in a different setting.

Interview with Eric P Winer, MD, July 6, 2010

Pertuzumab and Trastuzumab: Exploratory Biomarker Correlations with Clinical Benefit in Patients with Metastatic HER2-Positive Breast Cancer

Cortes J et al.

Proc ASCO 2010;Abstract 1066.

Introduction

- Pertuzumab (P) is a monoclonal antibody targeted against HER2 that prevents HER2 dimerization and induces antibody-dependent cell-mediated cytotoxicity.
- P monotherapy demonstrated activity against HER2-positive breast cancer (BC), although combination with trastuzumab (H) enhanced the antitumor effect of P (*Cancer Res* 2009;69:9330).
- Phase II trial of P and H combination therapy in patients with HER2-positive BC that had progressed on prior H therapy demonstrated a clinical benefit rate (CBR) of 50% and an objective response rate (ORR) of 24.2% (*J Clin Oncol* 2010;28:1138).
- **Current study objective:**
  - Evaluate a set of biomarkers for their prognostic or predictive utility for patients with HER2-positive metastatic BC (mBC) treated with P and H.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

Research To Practice®

Trial Schema

Eligibility (N = 66)

HER2-positive metastatic breast cancer

Progression on trastuzumab-based therapy as last treatment for metastatic disease

Measurable disease at baseline

Tumor samples collected at the time of primary surgery

→

P + H

P 840 mg loading dose → 420 mg q3w

H 4 mg/kg loading dose → 2 mg/kg weekly or 8 mg/kg loading dose → 6 mg/kg q3w

Protein and mRNA levels of potential prognostic or predictive significance were measured using immunohistochemistry and/or quantitative RT-PCR, immunoassay or FISH.
mRNA levels were used to divide patients into low HER2 expression (<median) and high HER2 expression (≥median) groups.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

Research To Practice®

Summary and Conclusions

- Exploratory biomarker analyses demonstrated:
  - Low HER2 mRNA expression was significantly correlated with higher ORR (p = 0.0046) and CBR (p = 0.0014) and improved progression-free survival (PFS) (p = 0.0082) compared to higher mRNA expression levels.
  - ORR for patients with HER2-positive BC was not correlated to levels of HER2 protein.
  - HER2 and HER3 mRNA levels were correlated to one another.
  - Low HER3 mRNA levels were associated with a less pronounced correlation with improved ORR, CBR and PFS.
- Further investigation of these biomarkers is warranted to advance the prediction of efficacy endpoints.

Cortes J et al. *Proc ASCO* 2010;Abstract 1066.

Research To Practice®