Trastuzumab-DM1 (T-DM1) in HER2-Positive Metastatic Breast Cancer
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 more than 30,000 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 OBJECTIVE

• Recall the mechanism of action and early clinical activity of trastuzumab-DM1.

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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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Advisory Committee: Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis; Consulting Agreement: Amgen Inc; Paid Research: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Onyx Pharmaceuticals Inc.

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Honoraria: Genentech BioOncology, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis; Paid Travel: Genentech BioOncology, Roche Laboratories Inc, Sanofi-Aventis; Stock Ownership: Amgen Inc, Pfizer Inc, Schering-Plough Corporation.

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Expiration date: August 2010
There’s a good reason that breast cancer occupies such an important position in cancer research and why oncologists’ interest in CME related to this illness seems unquenchable. Up to a third of patients in oncology waiting rooms are there for treatment of this disease and even laypeople can accurately speculate the likely cause of death when a young woman is listed in an obituary.

But are we moving forward quickly enough in a disease that is wreaking havoc on our grandmothers, mothers, sisters, wives and daughters? As I listened to the eight highly regarded breast cancer clinical investigators who participated in our CME group’s recent annual post-ASCO Think Tank review the best from Orlando, I found myself once again thinking more needs to get done, and soon.

While the PARP inhibitor story is reason for optimism, the following four papers/issues are evidence that there hasn’t been a whole lot of other new breast cancer stuff to get excited about in 2009.

We first cover two oral presentations with conflicting results that fail to clarify the role of CYP2D6 in the selection of hormonal therapy, and specifically the use of tamoxifen. While it now obviously makes sense to exercise caution when prescribing antidepressants to patients receiving TAM, the current utility of CYP2D6 testing remains controversial and is generally not recommended by investigators.

Similarly, our Think Tank faculty was largely underwhelmed by an ASCO paper attempting to correlate the results of the 70-gene MammaPrint assay with benefit from adjuvant chemo. It seems that the evidence base with MammaPrint may not be of the quality currently seen with Oncotype DX®, and further complicating the use of this assay is the fact that fresh-frozen tissue is required.

Click here for our slides and comments on CYP2D6 and MammaPrint.
Another important ASCO paper was presented by my mentor, Charles Vogel, who followed up on the exciting San Antonio findings with T-DM1, a trastuzumab/chemo conjugate that has produced stunning results in patients with extensive prior anti-HER treatment. Not much new was reported in Chuck’s presentation of this more mature data set, and clinicians will need to patiently wait as the process leading to approval and availability of this fascinating agent moves ahead at a snail’s pace.

**Click here for our slides and comments on trastuzumab-DM1.**

Data from another intriguing anti-HER therapy, pertuzumab, were also presented at ASCO, and while the mechanism of action (inhibition of HER2 dimerization) is interesting, our Think Tank faculty agreed that this agent will not likely become a part of nonprotocol treatment until, and maybe unless, Sandy Swain’s CLEOPATRA study (chemo/trastuzumab alone or with pertuzumab as first-line treatment of advanced disease) reports positive results. While anti-HER2 treatment is certainly the most exciting current corner of breast cancer, unfortunately it only impacts the estimated 20 percent of patients with HER2-positive tumors...or does it?

**Click here for our slides and comments on pertuzumab.**

This brings us to what might be considered the most exciting non-PARP moment in breast cancer this year, and it happened not at ASCO but during our Think Tank when Chuck Geyer answered a question I had eagerly awaited asking since exchanging a series of emails in May with his NSABP colleague, Soon Paik.

I reached out to Dr Paik for further clarification just after completing an interview with HER2 pathology maven Michael Press for our Breast Cancer Update audio series. During our conversation, Dr Press was highly critical of the NSABP’s subanalysis of patients in their B-31 adjuvant trastuzumab study who were initially believed to have HER2-positive tumors (thus entered on the study), but on central repeat the assays were read by Dr Paik as clearly HER2-negative by both IHC and FISH central testing.

In perhaps the world’s record for findings that were counterintuitive, these patients were also found to benefit from adjuvant trastuzumab perhaps even more so than the rest of the patients in the trial. Dr Press’s blood pressure seemed to escalate quickly when I asked him to speculate about the validity of this data set, and he and others contend that the findings may be the result of a problem with the central assays.
However, Dr Paik let me know that a “round-robin” was being conducted by three outside reference labs to confirm or refute this work, and this set of second opinions was due to be completed this summer.

So holding my breath, and with Dennis Slamon, Cliff Hudis and Harold Burstein ready to respond (pounce), I asked Dr Geyer if the round-robin was complete.

[Click here to see his amazing answer and the reaction of our faculty.]

Next up on 5-Minute Journal Club: Four interesting papers from the world of gynecologic oncology.

Neil Love, MD
Research To Practice
Miami, Florida
Trastuzumab-DM1 (T-DM1) in HER2-Positive Metastatic Breast Cancer

Presentation discussed in this issue:


Slides from the presentation and excerpts from a related “Think Tank” (July 24, 2009) featuring Clifford Hudis, MD and Dennis J Slamon, MD, PhD
Introduction

- Trastuzumab-DM1 (T-DM1) is a novel anti-HER2 antibody drug conjugate in development for HER2-positive metastatic breast cancer (MBC)
- T-DM1 combines the HER2-targeting properties of trastuzumab with targeted delivery of a highly potent anti-microtubule derivative, DM1

**Current study objectives:**

- Assess the objective response rate (ORR) and progression-free survival (PFS) of T-DM1 by independent radiologic review and investigator assessment in patients with HER2-positive MBC with disease progression on HER2-directed therapy
- Characterize safety and tolerability of T-DM1 in this patient population
- Characterize the pharmacokinetics of T-DM1

Source: Vogel CL et al. ASCO 2009; Abstract 1017.

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**Trastuzumab-DM1**

DM1 is a highly potent antimicrotubule agent

T-DM1 undergoes receptor-mediated internalization

Free DM1 is released within the cell

Source: Adapted with permission from Mackey JR. Discussant, ASCO 2009 Metastatic Breast Cancer Poster Discussion.
**Study Description**

- A multi-institutional, open-label, single-arm Phase II US study in patients with locally confirmed HER2-positive MBC with disease progression while receiving HER2-directed therapy
  - All patients received prior trastuzumab
    - Median 18 months of therapy
  - 67/112 (59.8%) patients also received prior lapatinib
    - Median 6 months of therapy
  - T-DM1 (3.6 mg/kg) was administered by IV infusion over 30–90 minutes every 3 weeks (q3w)

Source: Vogel CL et al. ASCO 2009; Abstract 1017.

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**Anti-Tumor Activity in All Treated Patients (n=112)**

<table>
<thead>
<tr>
<th></th>
<th>IRF N (%)</th>
<th>Investigator N (%)</th>
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<tbody>
<tr>
<td><strong>Best Objective Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>PR</td>
<td>28 (25.0%)</td>
<td>40 (35.7%)</td>
</tr>
<tr>
<td>SD</td>
<td>54 (48.2%)</td>
<td>43 (38.4%)</td>
</tr>
<tr>
<td>PD</td>
<td>21 (18.8%)</td>
<td>22 (19.6%)</td>
</tr>
<tr>
<td>Unable to evaluate</td>
<td>9 (8.0%)</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>28 (25.0%)</td>
<td>43 (38.4%)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate</strong></td>
<td>39 (34.8%)</td>
<td>50 (44.6%)</td>
</tr>
</tbody>
</table>

CR, complete response; IRF, independent review facility; PR, partial response; PD, progressive disease; SD, stable disease
* Includes patients who achieved CR, PR or SD ≥ 6 months

Source: Vogel CL et al. ASCO 2009; Abstract 1017.
Progression-Free Survival: No Difference Between IRF* and Investigator Assessment

*IRF = Independent review faculty; INV = Investigator
Source: With permission from Vogel CL. ASCO 2009; Abstract 1017.

ORR in Efficacy-Evaluable* Centrally Confirmed HER2-positive Patients

<table>
<thead>
<tr>
<th>Assessment</th>
<th>IRF N = 75</th>
<th>Investigator N = 75</th>
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<tr>
<td>Patients with OR, n (%) 95% CI for OR</td>
<td>24 (32.0%)</td>
<td>36 (48.0%)</td>
</tr>
<tr>
<td></td>
<td>22.1% – 43.0%</td>
<td>36.3% – 59.9%</td>
</tr>
<tr>
<td>Patients with Clinical Benefit†, n (%) 95% CI for Clinical Benefit</td>
<td>33 (44.0%)</td>
<td>41 (54.7%)</td>
</tr>
<tr>
<td></td>
<td>33.2% – 55.5%</td>
<td>43.0% – 66.2%</td>
</tr>
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</table>

CI, confidence interval; OR, objective response
* 75 of the 112 patients who either received one or more doses of T-DM1 and had one or more post-baseline tumor assessment or died on therapy
† Includes patients who achieved CR, PR or SD ≥ 6 months

Source: Vogel CL et al. ASCO 2009; Abstract 1017.
Most Common Grade 3/4 Adverse Events and Cardiac Function

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 3 N (%)</th>
<th>Grade 4 N (%)</th>
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<tbody>
<tr>
<td>All Grade 3/4 Adverse Events</td>
<td>42 (37.5%)</td>
<td>14 (12.5%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9 (8.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (4.5%)</td>
<td>3 (2.7%)</td>
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- No Grade $\geq$ 3 LVEF events (symptomatic congestive heart failure and/or LVEF of <40%) were observed
- Two patients had declines in LVEF to below 45%; neither required discontinuation of study drug

Source: Vogel CL et al. ASCO 2009; Abstract 1017.

Summary and Conclusions

- T-DM1 at 3.6 mg/kg has robust single-agent activity in patients with previously treated HER2-positive MBC as measured by ORR, duration of response, and PFS
  - T-DM1 demonstrated similar anti-tumor activity in patients previously treated with both lapatinib and trastuzumab (data not shown)
- HER2-positivity (centrally confirmed) was strongly correlated with objective response
- T-DM1 is well tolerated by patients at the dose and schedule tested with no dose-limiting cardiotoxicity
- T-DM1 is currently being studied in patients with HER2-positive MBC in Phase I through III trials

Source: Vogel CL et al. ASCO 2009; Abstract 1017.
CLIFFORD HUDIS, MD: T-DM1 is trastuzumab chemically linked to the maytansine derivative DM1, which is an antimicrotubule agent. DM1 in its native form is too toxic for significant dosing at the systemic level, but when delivered attached to trastuzumab, it is essentially a high-tech homing device to the tumor cell. The mechanism of action is thought to be dependent on the endocytosis of the receptor/antibody complex followed by cleavage of the linkage molecule releasing the chemotherapy intracellularly. This is a concept people have dreamt of for years in terms of targeted therapy.

The confirmed PR-CR rate in this study, as determined by independent review, was about 25 percent. What is striking about this result is the fact that this patient population was 100 percent pretreated with trastuzumab, with 60 percent of patients also pretreated with lapatinib. Whether this is a direct HER2 suppression effect or simply a way of delivering a chemotherapy agent directly into specific cells remains to be determined. This does suggest, however, that continuing to target HER2 in one form or another can be useful. The development of this agent is moving forward quickly.

DR LOVE: Dennis, what research strategies should be implemented with this agent?

DENNIS J SLAMON, MD, PhD: The number of options now available to patients with HER2-positive disease is enormous. With T-DM1, you’re delivering the cytotoxic agent directly to the HER2-positive cells. Past strategies for linking such conjugates failed because the linkers came apart. A new technology was utilized to ensure that the trastuzumab-DM1 conjugate remains together until it’s delivered to the tumor cell, and the T-DM1 data in recurrent disease looked pretty spectacular relative to retreating with trastuzumab or even moving to lapatinib. The safety data also look good thus far. The unique mechanism of action may mean that T-DM1 could be superior to single-agent trastuzumab, and there needs to be a head-to-head comparison against the parent molecule, trastuzumab and also against lapatinib.

Dr Hudis is Chief of Breast Cancer Medicine Service at the Solid Tumor Division in the Department of Medicine at the Memorial Sloan-Kettering Cancer Center in New York, New York.

Dr Slamon is Professor of Medicine and Chief of the Division of Hematology/Oncology as well as Director of Clinical/Translational Research at the Jonsson Comprehensive Cancer Center at the David Geffen School of Medicine at UCLA in Los Angeles, California.