

POST-SABCS Issue 2, 2013

Pooled Safety Analysis of T-DM1 in 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. This unique conference provides many clinicians and scientists from around the world a forum for discussing critical issues in the prevention and management of breast cancer. Therefore, SABCS is targeted by many members of the clinical research community as the optimal time to unveil new clinical data. This creates an environment in which yearly published results from a plethora of ongoing clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes.

Although SABCS currently offers online access to the vast majority of the poster and plenary presentations from the annual meeting, the absence of expert assessment concerning practical applications may yield confusion among community oncologists who are challenged almost daily to appropriately apply a multitude of scientific findings across diverse tumors. Thus, identification of those data sets with immediate or impending relevance to the delivery of quality breast cancer care, in conjunction with professional commentary to address resultant practice ambiguity, may prove vastly beneficial to those physicians who are unable to make the annual pilgrimage to San Antonio. 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, including expert perspectives on how these new evidence-based concepts can and should be incorporated into on- and off-protocol patient care. This activity will assist medical oncologists, radiation oncologists, breast/general surgeons, nurses and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings from the second interim survival analysis of the CLEOPATRA study and the subset analysis of patients based on age, and apply this information to the treatment of patients with metastatic HER2-positive breast cancer.
- Recall the benefits and risks of combining HER2-targeted antibodies with chemotherapeutic agents for the treatment of HER2positive advanced breast cancer.
- Understand the association between PI3 kinase mutational status and prognosis in patients with HER2-positive metastatic breast cancer.
- Evaluate the efficacy and safety of adding eribulin mesylate to trastuzumab for patients with HER2-positive advanced breast cancer.
- Compare the toxicity profile of T-DM1 across multiple studies in metastatic HER2-positive breast cancer, and consider this
 information in the selection of optimal HER2-targeted later-line 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:

José Baselga, MD, PhD Physician-in-Chief Memorial Sloan-Kettering Cancer Center New York, New York

Consulting Agreements: Genentech BioOncology, Novartis Pharmaceuticals Corporation.

Kimberly L Blackwell, MD Professor of Medicine Director, Breast Cancer Program Duke Cancer Institute Durham, North Carolina

Advisory Committee: Novartis Pharmaceuticals Corporation; Consulting Agreements: Novartis Pharmaceuticals Corporation, Sandoz; Contracted Research: Celgene Corporation, Genentech BioOncology, Roche Laboratories Inc; Speakers Bureau: Genomic Health Inc. Lisa A Carey, MD Richardson and Marilyn Jacobs Preyer Distinguished Professor for Breast Cancer Research Chief, Division of Hematology and Oncology Physician-in-Chief North Carolina Cancer Hospital Associate Director for Clinical Research Lineberger Comprehensive Cancer Center Chapel Hill, North Carolina

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Edith A Perez, MD Deputy Director at Large, Mayo Clinic Cancer Center Group Vice Chair, Alliance of Clinical Trials in Oncology Serene M and Frances C Durling Professor of Medicine Mayo Clinic Jacksonville, Florida Contracted Research: Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline.

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Hardware/Software Requirements: A high-speed Internet connection A monitor set to 1280 x 1024 pixels or more Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later Adobe Flash Player 10.2 plug-in or later Adobe Acrobat Reader (Optional) Sound card and speakers for audio

Last review date: March 2013 Expiration date: March 2014



POST-SABCS Issue 2, 2013

The new world of HER2-positive breast cancer

To go directly to slides and commentary for this issue, click here.

Last week I met with the new Physician-in-Chief at Memorial Sloan-Kettering Cancer Center, Dr José Baselga, and after talking a bit about his vision for the future of that preeminent institution we focused on a corner of oncology he has influenced mightily throughout his career, breast cancer research. Not surprisingly, we spent much of our time reviewing anti-HER2 treatment — which has witnessed the FDA approval of 2 new agents in the past 9 months. Dr Baselga got things started by commenting on the Phase III trial he chaired, CLEOPATRA, which clearly demonstrated a substantial boost in efficacy when the HER2 dimerization inhibitor pertuzumab (P)



José Baselga, MD, PhD RTP Studios (3-9-2013)

was added to docetaxel and trastuzumab (T) as first-line therapy for metastatic HER2positive disease. In the trial progression-free survival (PFS) increased from 12.4 to 18.5 months with a similar safety profile, and although the magnitude of this landmark finding surprised many observers, Dr Baselga stated that he fully expected the results based on the substantial antitumor activity seen when P was added to T in patients with disease progression on T in a prior Phase II trial.

We then chatted about the antibody-drug conjugate trastuzumab emtansine (T-DM1) and the EMILIA trial that exploded onto the scene during the ASCO 2012 plenary session, revealing T-DM1's clear-cut superiority in both efficacy (PFS and overall survival) and tolerability over an established and frequently used regimen (capecitabine/lapatinib) among patients who had previously been treated with T + a taxane. As the agent was just approved 2 weeks before the interview, our conversation took on a different tone, as for the first time I was able to ask an investigator the practical (rather than hypothetical) question of current sequencing of therapy for metastatic HER2-positive disease. Dr Baselga, in commenting on this complex issue that has likely been discussed at every tumor board on the planet, slowly removed his eyeglasses, carefully put them on the desk, thought for a moment and then voiced his perspective, which is similar to those I have heard recently from Dr Eric Winer and others: "Some people are so excited about T-DM1 that they want to use it first line, but I think this is a time for intellectual calm. Right now, trastuzumab, pertuzumab and a taxane is our standard first-line treatment, with T-DM1 as second line."

For the record, he and his Memorial colleagues usually choose paclitaxel as a partner for T + P, partially based on the reassuring Phase II data the group reported at San Antonio with this regimen. As I have been known to do, I tried to push Dr Baselga a bit regarding his strong feeling not to use T-DM1 first line and asked him how he would approach an 85-year-old patient with ER-negative, HER2-positive metastatic breast cancer for whom traditional chemotherapy might be out of place. He, however, stuck to his guns, commenting that a short taxane course (with T + P) in many fit, older patients is a well-tolerated life investment that results in a median progression-free interval of 18 months.

Whatever the algorithm is for now, it may very well change in a year or so when the MARIANNE study reports. This crucial Phase III first-line trial compares T + a taxane to T-DM1 alone or with P. Dr Baselga very clearly stated his opposition to the nonprotocol use of T-DM1 combined with P until more trial data become available, and other investigators, including Dr Winer, have done the same.

Of course, many other complex questions remain about the treatment of metastatic HER2-positive breast cancer, and below we review some of the more interesting efforts unveiled in San Antonio that attempt to provide needed answers:

1. More from the CLEOPATRA trial: Overall survival benefit; biomarker analysis; effects in older patients

With 154 deaths in the control group and 113 in the T + P + docetaxel arm, <u>the study</u> has now allowed crossover to P. In terms of biomarkers, according to Dr Baselga, who presented <u>these data</u> in San Antonio, perhaps the key factor moving forward will be the identification of PI3-kinase mutations in approximately 25% of HER2-positive tumors and the potential use of PI3-kinase alpha inhibitors, which are currently being evaluated. Finally, although only 126 patients in <u>CLEOPATRA</u> were older than age 65, the benefit they derived from treatment was similar to what was seen with younger patients.

2. Choice of chemotherapy to combine with T + P

Referred to earlier, a **San Antonio report** from Memorial demonstrated a 76% 6-month PFS rate in 33 evaluable patients receiving T + P + weekly paclitaxel. No unexpected toxicities were encountered, and this work provides additional strength to the conclusion everyone, including the NCCN, had already reached, namely that paclitaxel is a reasonable agent to combine with T and P. To obtain more real-world perspectives on this issue, an international single-arm study (**PERUSE**) is now evaluating T + P with 3 different taxanes (paclitaxel, *nab* paclitaxel and docetaxel).

3. Pooled safety analysis of single-agent T-DM1

These data from 882 patients on 6 clinical trials (including EMILIA) revealed few clinically apparent toxicities but did document transient laboratory abnormalities, such as thrombocytopenia and abnormal liver function tests, in a quarter or more of patients. Overall, treatment discontinuation due to toxicity was observed in only 55 patients (6.2%).

4. Eribulin combined with T

Indefinite anti-HER2 treatment is now a standard part of care for patients with HER2positive metastatic disease, and as new chemotherapy agents are developed, studies are needed to document whether these are safe and efficacious partners for T. <u>This</u> <u>report</u> of 40 patients demonstrated what most observers expected — efficacy similar to other chemotherapy/T combinations (55% CR + PR) and acceptable tolerability comparable to what has been reported with eribulin alone.

For the next issue of this series we review the many San Antonio papers on genomic markers, including yet another analysis with the 21-gene recurrence score in tumor specimens from a prior randomized adjuvant trial, in this case NSABP-B-28, which evaluated the addition of paclitaxel to AC.

Neil Love, MD **Research To Practice** Miami, Florida

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Pooled Safety Analysis of T-DM1 in HER2-Positive Metastatic Breast Cancer

Presentation discussed in this issue

Dieras V et al. **Trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2-positive metastatic breast cancer: Pooled safety analysis.** San Antonio Breast Cancer Symposium 2012; **Abstract P5-18-06**.

Slides from a presentation at SABCS 2012 and transcribed comments from an interview with Kimberly L Blackwell, MD (6/26/12)

Trastuzumab Emtansine in HER2-Positive Metastatic Breast Cancer: Pooled Safety Analysis from Seven Studies

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

Background

- Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) that inhibits HER2 signaling and induces antibodydependent cellular cytotoxicity.
- In a Phase III study, T-DM1 improved overall survival (OS) and progression-free survival (PFS) compared to lapatinib/ capecitabine in previously treated HER2-positive locally advanced or metastatic breast cancer (BC) (*NEJM* 2012;367:1783):
 - OS: 30.9 mo vs 25.1 mo (HR = 0.68; p<0.001)</p>
 - PFS: 9.6 mo vs 6.4 mo (HR = 0.65; p < 0.001)
 - Incidence of Grade ≥3 adverse events (AEs) was lower with T-DM1
- <u>Study objective</u>: To perform an integrated safety analysis of single-agent T-DM1 based on data from patients with unresectable locally advanced or metastatic BC.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.



Study Methods (Continued): Characteristics of Pooled Studies

- All studies assessed AEs, basic laboratory data, vital signs, physical examination findings and left ventricular ejection fraction (LVEF) per schedules.
- Laboratory assessments typically occurred weekly during the first several treatment cycles.
- AEs were graded according to the NCI-CTCAE v3.0 criteria.
- AEs were reported up to 30 days after the last dose of study medication, until early termination visit or at the initiation of another anticancer therapy, whichever occurred first.
- Afterward, investigators reported only deaths from any cause and serious AEs (SAEs) that were considered to be related to prior study treatment.
- All baseline characteristics excluding prior therapies were similar across studies.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

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Select AEs in Patients Who Received T-DM1 (Incidence ≥20%)

| n = 882 | Any grade | Grade 3 | Grade 4 |
|------------------|-----------|---------|---------|
| Fatigue | 45.4% | 3.1% | 0.1% |
| Nausea | 42.3% | 1.0% | 0% |
| Headache | 28.7% | 0.6% | 0% |
| Thrombocytopenia | 28.7% | 8.3% | 1.9% |
| Constipation | 25.5% | 0.6% | 0% |
| Increased AST | 23.0% | 4.0% | 0.1% |
| Diarrhea | 20.3% | 0.9% | 0% |
| Hypokalemia* | 14.4% | 2.9% | 0% |
| Increased ALT* | 15.2% | 2.8% | 0% |
| Anemia* | 13.7% | 2.5% | 0% |

* AEs with Grade 3 or 4 incidence $\geq 2\%$.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

Overview of AEs

- The most commonly reported AEs (any grade) were fatigue, nausea, headache, thrombocytopenia and constipation.
- With the exception of fatigue, the most commonly reported Grade ≥3 AEs were related to laboratory test abnormalities.
- A total of 55 patients (6.2%) discontinued T-DM1 due to AEs.
 - Most common AEs also responsible for dose reductions included mainly thrombocytopenia (1.4%) and increased AST/ALT (0.8%/0.5%).
- SAEs were reported in 18.6% of patients.
- During treatment or within 30 days of last T-DM1 dose, 9 patients experienced AEs leading to death.
 - Of these, 4 were deemed by the investigator to be T-DM1 related (hepatic failure, hepatic function abnormality, bacterial sepsis and metabolic encephalopathy).

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

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Hepatotoxicity

- The incidence of increased transaminases was similar across studies but slightly higher in Study B.
- Increases in mean AST and ALT were generally transient:
 - Proportion of patients with Grade ≥3 increased AST/ALT did not increase over time.
 - Most patients continued T-DM1 therapy after appropriate dose modifications.
- All-grade increases in serum bilirubin occurred in 24 patients. These were of Grade 3 in 3 patients, with no grade 4 events.
- Out of 882 patients, 3 cases of biopsy-confirmed nodular regenerative hyperplasia (NRH) were recorded; these patients had clinical or radiographic signs of portal hypertension.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

Thrombocytopenia

- This was the primary dose-limiting toxicity associated with T-DM1.
- Grade 3 or 4 thrombocytopenia generally occurred within cycles 1 and 2.
- Thrombocytopenia was not fully reversible in all patients, but with the appropriate dose modifications, platelet counts recovered sufficiently to allow treatment continuation.
- Of 122 patients with Grade 3 or 4 thrombocytopenia:
 - Grade 1 bleeding: 51 (41.8%)
 - Grade 2 bleeding: 4 (3.3%)
 - Grade 3 or 4 bleeding: 6 (4.9%)
- Grade 3 or 4 bleeding events and Grade 3 or 4 thrombocytopenia did not occur concurrently in any of the patients. Research

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

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Incidence of Thrombocytopenia and Hemorrhage (HMG) with T-DM1 by Grade (G)

| | Thrombocytopenia (n) | | | | | | | |
|-------|----------------------|-----|-----|-----|----|----|-------|--|
| HMG | GO | G1 | G2 | G3 | G4 | G5 | Total | |
| G0 | 125 | 280 | 115 | 54 | 7 | 0 | 581 | |
| G1 | 19 | 108 | 69 | 42 | 9 | 0 | 247 | |
| G2 | 2 | 17 | 16 | 4 | 0 | 0 | 39 | |
| G3 | 2 | 1 | 5 | 5 | 1 | 0 | 14 | |
| G4 | 0 | 1* | 0 | 0 | 0 | 0 | 1* | |
| G5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Total | 148 | 407 | 205 | 105 | 17 | 0 | 882 | |

* Patient had Grade 4 GI hemorrhage on study day 797 after the most recent T-DM1 dose, but the event resolved in a day and was considered to be unrelated to T-DM1.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

Cardiac Safety

- Cardiac dysfunction (SMQ-narrow; "cardiac failure") was infrequent: 1.5%
 - Majority of patients experienced Grade 1 or 2 events (11/13).
 - Two of 13 patients experienced Grade 3 decreased ejection fraction.
- Patients with a postbaseline LVEF <40%: 4 (0.5%)
- Patients with LVEF decline from baseline (≥15% to <50%): 16 (1.8%)
- Patients who discontinued T-DM1 due to cardiac disorders: 3 (0.3%):
 - Atrial fibrillation (n = 1)
 - Left ventricular dysfunction (n = 1)
 - Decreased ejection fraction (n = 1)

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

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Author Conclusions

- The safety profile was consistent across studies, and the most commonly reported Grade ≥3 AEs were thrombocytopenia (10.2%) and increased AST (4.1%).
- The majority of thrombocytopenia AEs were of Grade 1 or 2.
 - Six patients experienced Grade 3 or 4 thrombocytopenia and hemorrhage, but these AEs were not temporally related.
 - Whereas most Grade ≥3 thrombocytopenia did not fully recover to baseline, platelet counts recovered in nearly all patients, allowing treatment continuation.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

Author Conclusions (Continued)

- Increases in serum transaminases were generally transient, allowing patients to continue treatment at the same/reduced dose.
 - Three cases of NRH were reported among the 882 patients exposed to single-agent T-DM1; NRH should be considered if noncirrhotic portal hypertension occurs.
- The safety profile of T-DM1 is consistent with the theoretical concept underlying the design of ADCs — that targeting delivery of chemotherapy to tumors and restricting chemotherapy release to intracellular compartments reduces systemic toxicity.

Diéras V et al. Proc SABCS 2012; Abstract P5-18-06.

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Investigator Commentary: A Pooled Safety Analysis of T-DM1 in HER2-Positive Metastatic Breast Cancer

From our experiences with the EMILIA trial, T-DM1 is an easy drug to administer to patients. In this trial, the dose intensity for T-DM1 was 100%, so we are able to get this drug into patients well. The Grade 3 and 4 toxicities associated with the agent were mainly laboratory abnormalities such as elevations in AST and ALT liver enzymes. An unusual phenomenon described in other studies of T-DM1 is transient thrombocytopenia that usually occurs between days 8 and 10 of the treatment cycle. If you do not look for it between the 21-day treatment cycles, you might miss it. The cause of this transient thrombocytopenia is under investigation, but it is hypothesized that the agent must have some binding affinity to platelets.

As a practicing clinician, what is meaningful about the toxicities associated with T-DM1 that we observed on the EMILIA trial is that they did not affect the patient's quality of life. I believe T-DM1 is an active agent that appears to be superior to lapatinib and capecitabine in terms of survival. It may be what we have been searching for — a cancer treatment without the side effects of chemotherapy.

Interview with Kimberly L Blackwell, MD, June 26, 2012