5 Minute JournalClub

POST-SABCS Issue 2, 2013

Phase IIIb PERUSE Study of Pertuzumab, Trastuzumab and a Taxane for HER2-Positive Advanced 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 HER2-positive 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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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

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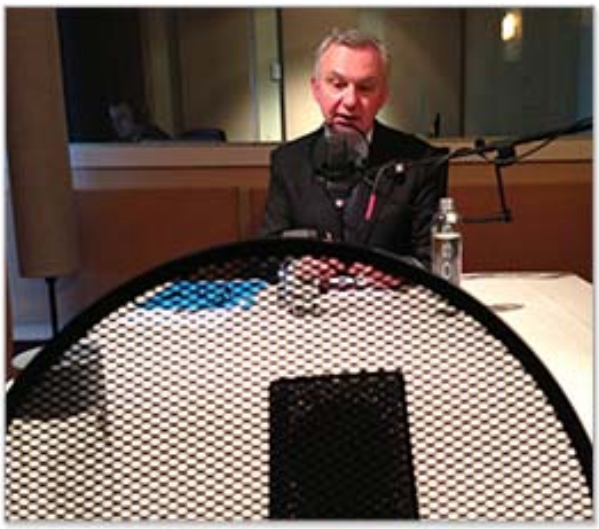
POST-SABCS Issue 2, 2013

The new world of HER2-positive breast cancer

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



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

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) was added to docetaxel and trastuzumab (T) as first-line therapy for metastatic HER2-positive 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, **the study** has now allowed crossover to P. In terms of biomarkers, according to Dr Baselga, who presented **these data** 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 **CLEOPATRA** 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 HER2-positive metastatic disease, and as new chemotherapy agents are developed, studies are needed to document whether these are safe and efficacious partners for T. **This report** 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.

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Phase IIIb PERUSE Study of Pertuzumab, Trastuzumab and a Taxane for HER2-Positive Advanced Breast Cancer

Presentation discussed in this issue

Bachelot T et al. **A single-arm Phase IIIb study of pertuzumab and trastuzumab with a taxane as first-line therapy for patients with HER2-positive advanced breast cancer (PERUSE).** San Antonio Breast Cancer Symposium 2012;**Abstract OT1-1-02**.

Slides from a presentation at SABCS 2012 and transcribed comments from a recent interview with Edith A Perez, MD (1/17/13)

Background

- Pertuzumab (P) is a HER2 heterodimerization inhibitor that recognizes an epitope on HER2 distinct from that bound by trastuzumab (H); hence their complementary mechanisms of action result in a more comprehensive HER2 blockade.
- The Phase III CLEOPATRA trial reported significantly improved PFS in patients (pts) receiving P + H + docetaxel versus H + docetaxel as first-line treatment for HER2-positive metastatic breast cancer (BC) (*NEJM* 2012; 366:109).
- **Study objective:** This ongoing trial will evaluate the safety and efficacy of P + H with one of a choice of taxanes as first-line therapy for patients with HER2-positive advanced BC.

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

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PERUSE Key Eligibility Criteria

Eligibility (N = 1,500*)
Women/men with HER2+ advanced BC (metastatic or locally recurrent)
No prior systemic antihormonal therapy in the metastatic setting
Prior (neo)adjuvant H and/or lapatinib allowed if no disease progression during treatment
Disease-free interval ≥6 mo
ECOG PS 0-2
LVEF ≥50%
No clinical or radiographic evidence of CNS metastases or clinically significant cardiovascular disease
No other malignancy in the past 5 y except carcinoma in situ of the cervix or basal cell carcinoma

* To be enrolled over 18 mo; first patient enrolled on May 31, 2012

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

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PERUSE Phase IIIb Study Design

- Global, open-label, single-arm, Phase IIIb study (NCT01572038)
- Therapy: P + H + taxane (docetaxel or paclitaxel or *nab* paclitaxel, by choice of investigator)
  - P: 840 mg initial dose, 420 mg maintenance, IV, q3wk
  - H: 8 mg/kg initial dose, 6 mg/kg maintenance, IV, q3wk
  - Taxane: According to local guidelines
  - Cycle 1: P d1, H d2; other cycles: P, H, taxane, in any order
- Patients with hormone receptor-positive disease can receive endocrine therapy with P + H after completion of taxane therapy.
- P will be provided to pts still receiving the investigational agent at study end who are eligible to enter an extension study to collect safety data and prespecified efficacy measures.

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

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Study Endpoints

Primary endpoint:

- Safety and tolerability

Secondary endpoints:

- Progression-free survival
- Overall survival
- Overall response rate
- Clinical benefit rate
- Duration of response
- Time to response
- Health-related quality of life

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

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Planned Analyses

- Primary analysis will be of Grade ≥3 adverse events (AEs) related to pertuzumab.
- Further analysis of safety endpoints will include incidence and severity of all AEs and serious AEs, cause of death, premature discontinuation from study, incidence of congestive heart failure, LVEF over the course of the study and laboratory test abnormalities.
- The incidence of select safety variables will be analyzed overall and by subgroups (country, age, ECOG performance status and type of taxane).
- Best overall response will be assessed by number and proportion of responders and nonresponders, together with 2-sided 95% confidence intervals.

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

Planned Analyses (Continued)

- Incidence of baseline covariates on overall response rate will be analyzed in an exploratory manner.
- All pts will be followed until final analysis, to be done 45 mo after the last pt has been enrolled or all pts in the study have withdrawn consent or died or if the study is prematurely terminated, whichever occurs first.
- In addition to the final analysis, 5 interim analyses for safety and efficacy are planned after enrollment of 100, 350, 700, 1,100 and 1,500 pts. Results will be reviewed by an Independent Data Monitoring Committee.

Bachelot T et al. *Proc SABCS* 2012;Abstract OT1-1-02.

Investigator Commentary: Ongoing Phase IIIb PERUSE Study of Pertuzumab and Trastuzumab with a Taxane as First-Line Therapy for Patients with HER2-Positive Advanced Breast Cancer

The CLEOPATRA study demonstrated a significant improvement in progression-free survival and an overall survival benefit when patients with HER2-positive metastatic breast cancer received pertuzumab and trastuzumab in combination with docetaxel. Based on these results, it is logical for continued research investigating anti-HER2 antibodies in combination with other taxanes and nontaxane agents to maintain efficacy while minimizing toxicity for patients. Several Phase II trials are evaluating combinations of new agents with pertuzumab and trastuzumab. This is good science to follow, and I would enroll patients on this ongoing trial.

Interview with Edith A Perez, MD, January 17, 2013

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