5 Minute JournalClub

POST-SABCS Issue 5, 2013

Final Planned Joint Analysis of Overall Survival from NSABP-B-31 and NCCTG-N9831

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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

- Determine the optimal duration of trastuzumab administration in the adjuvant setting using recent clinical trial evidence evaluating 1 year of adjuvant trastuzumab versus 6 months or 2 years.
- Assess the long-term survival outcomes of patients receiving 1 year of adjuvant trastuzumab combined with chemotherapy in comparison to those receiving only chemotherapy, and consider this information in the management of early HER2-positive breast cancer.
- Evaluate the association between immune biomarkers and clinical responses to trastuzumab and pertuzumab as support for the potential use of combined HER2-targeted and immunomodulatory agents.

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This activity is supported by educational grants from Eisai Inc, Genentech BioOncology and Genomic Health Inc.

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: May 2013
Expiration date: May 2014

5 MinuteJournalClub

POST-SABCS Issue 5, 2013

Key Papers on Adjuvant and Neoadjuvant Treatment of HER2-Positive Breast Cancer

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

It's now coming up on 8 years since that warm May day in Orlando when Dr George Sledge chaired the historic ASCO session during which the very first Phase III data sets confirming the benefit of adjuvant trastuzumab (T) with chemotherapy were unveiled. In San Antonio this past December we witnessed perhaps the final meaningful remnants of that generation of landmark studies while also getting a peek at the next set of relevant issues currently being addressed in ongoing trials. So to close out this year's SABCS highlights series we look at several of the most intriguing presentations focused on the management of early HER2-positive disease.

1. Duration of adjuvant trastuzumab: HERA and PHARE trials

During a CME symposium our group hosted on the first night of the conference, the ever-mirthful Dr Sledge was tasked with reviewing this pragmatic topic, and to get things started the first slide he showed was a beautiful photo of the earth orbiting the sun. Of course, Dr Sledge's visual metaphor related to the conclusion that he and most investigators had come to accept following the presentations of the HERA and PHARE data sets last October at the 2012 European Society for Medical Oncology Congress in Vienna — that 1 year of adjuvant T remains the optimal duration.

Both of these studies were updated in San Antonio. HERA, presented by Dr Martine Piccart-Gebhart, provided a definitive answer that 2 years of T is not better than 1. On the other hand, the French PHARE trial attempted to build on the signal observed in the underpowered but encouraging FinHer study of 9 weeks of T and compared 6 months to 12 months. During the presentation at San Antonio I got lost in terms like "failed to prove lack of inferiority," but just looking at the numbers, 6 months didn't look quite as efficacious as 12, and the collective sentiment appears to be that we've done the right thing all along by following Dr Sledge's orbital concept.

2. Long-term impact of adjuvant trastuzumab

In a brilliant and detailed analysis presented to the FDA in early 2005, the late NSABP statistician Dr John Bryant proposed that combining the data from 2 ongoing simultaneous adjuvant T trials (NSABP-B-31 and NCCTG-N9831) not only was feasible but also would help to obtain a quicker answer for patients, particularly as clinicians in practice grew increasingly uncomfortable holding the line at not using this relatively nontoxic agent with such a great likelihood of success. The FDA agreed with this premise, and later that year I had the pleasure of interviewing the NSABP's Dr Edward Romond just moments after his presentation to the ASCO multitudes of this combined data set. During this memorable conversation Dr Romond's voice was tremulous with emotion as he recounted for our audio audience the amazing history leading to that moment.

Dr Romond was again center stage in San Antonio, presenting the 10-year survival data from that landmark combined effort. The data reveal that the effects of treatment were similar regardless of ER status (this was also seen in HERA) and the survival benefit was still maintained although somewhat attenuated due to crossover to T once the data were released (20% crossover in the NSABP/NCCTG data and an unprecedented 52% in HERA). However, the profound impact of this advance can be understood from a different perspective when we consider the final numbers from this analysis of 4,046 patients: 391 vs 227 patients with distant recurrence; 381 vs 234 deaths from breast cancer; 206 vs 137 deaths among patients with ER and/or PR-positive tumors; 212 vs 149 deaths among patients with ER and PR-negative tumors.

3. The way forward? Initial evidence suggesting a potential future role for immune checkpoint inhibitors combined with anti-HER2 agents

As this first adjuvant HER2 chapter closes, others on the horizon will soon open, and when one asks investigators which current study or concept seems most promising, the first response is quite frequently the classically straightforward but immensely interesting APHINITY trial comparing adjuvant chemotherapy/T with or without the HER2 dimerization inhibitor pertuzumab. The enthusiasm for this compelling concept is partially related to prior data from the Phase II NeoSphere trial presented by Dr Luca Gianni, which demonstrated a marked increase in pathologic CRs when pertuzumab was added to chemotherapy/T in the neoadjuvant setting.

As in many contemporary neoadjuvant trials, a critical component of NeoSphere was the collection and analysis of tumor tissue, and at San Antonio Dr Gianni presented thought-provoking findings that expression of immune-based biomarkers, including PD-1, PD-L1, CTLA-4 and others, may predict benefit from HER2-directed therapies. These hypothesis-generating data may open the door to a new frontier in which anti-HER2 therapy is combined with the immune modulators that are offering so much hope

in melanoma, renal cell carcinoma, lung cancer and other challenging neoplasms. It will be fascinating to compare the NeoSphere translational findings to those about to be presented with the very first oral breast cancer paper at the upcoming ASCO meeting by Dr Lisa Carey from a major CALGB neoadjuvant HER2 study that also includes extensive tissue correlates.

This concludes our annual San Antonio wrap-up. Keep an eye out for our upcoming pre-ASCO email/video program with highlights from a recent breast cancer clinical investigator Think Tank with more on these and other new data sets and trial concepts.

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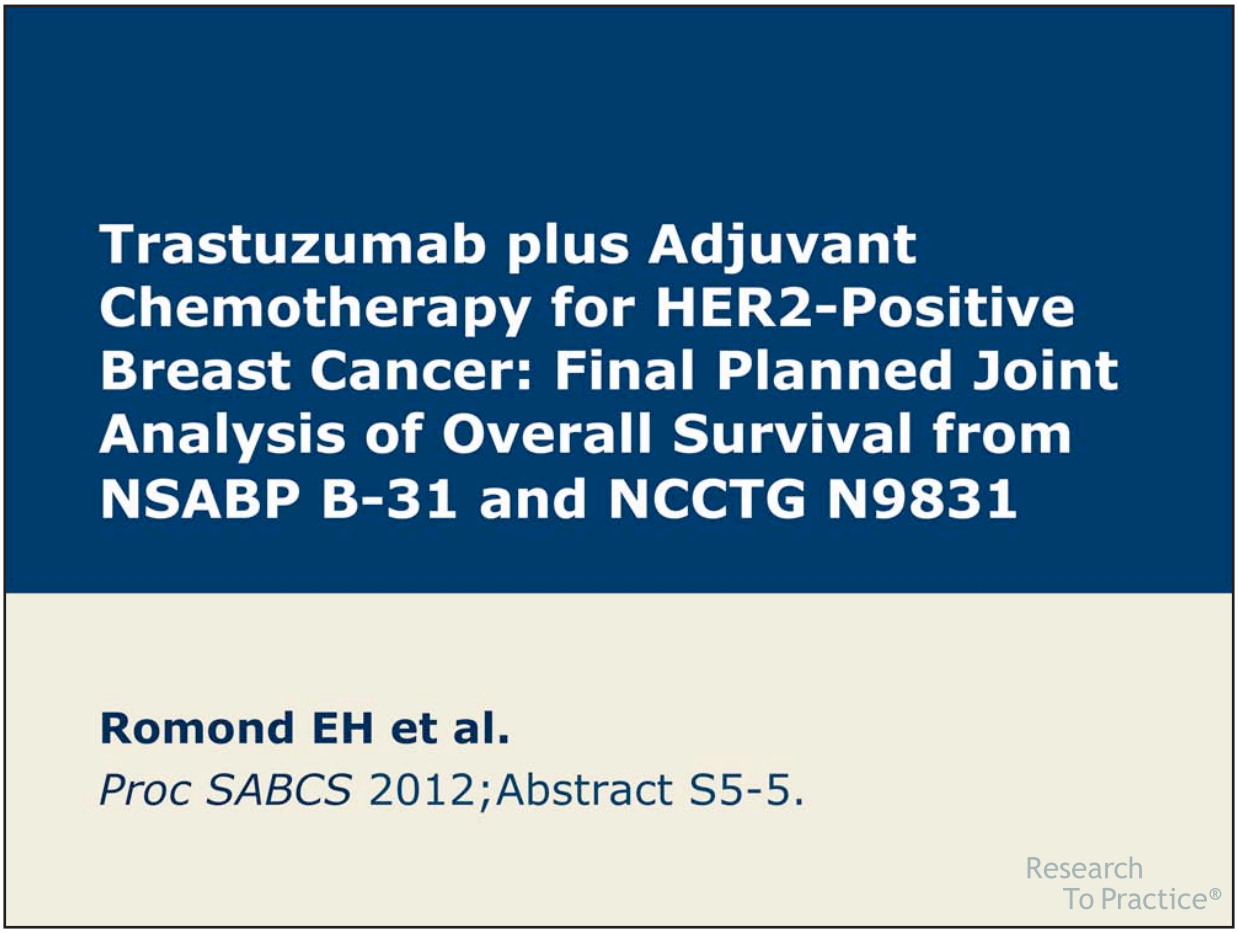
Final Planned Joint Analysis of Overall Survival from NSABP-B-31 and NCCTG-N9831

Presentation discussed in this issue

Romond E et al. **Trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer: Final planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831.** San Antonio Breast Cancer Symposium 2012;**Abstract S5-5**.

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



Background

- NSABP-B-31 and NCCTG-N9831 are 2 parallel clinical trials investigating the use of paclitaxel and trastuzumab after anthracycline chemotherapy for the adjuvant treatment of high-risk HER2-positive breast cancer.
- The first interim analysis was presented with a median follow-up of 2 years (*NEJM* 2005;353:1673).
  - Reduction in disease-free survival: 52%
  - Reduction in mortality: 33%
- **Current study objective:** Report the survival results of the final planned joint analysis of NSABP-B-31 and NCCTG-N9831.

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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NSABP-B-31 and NCCTG-N9831 Study Arms

= doxorubicin/cyclophosphamide (AC) 60/600 mg/m^2 q3wk x 4

= paclitaxel (P) 175 mg/m^2 q3wk x 4

= paclitaxel (P) 80 mg/m^2 qwk x 12

= trastuzumab (H) 4 mg/kg LD + 2 mg/kg qwk x 51

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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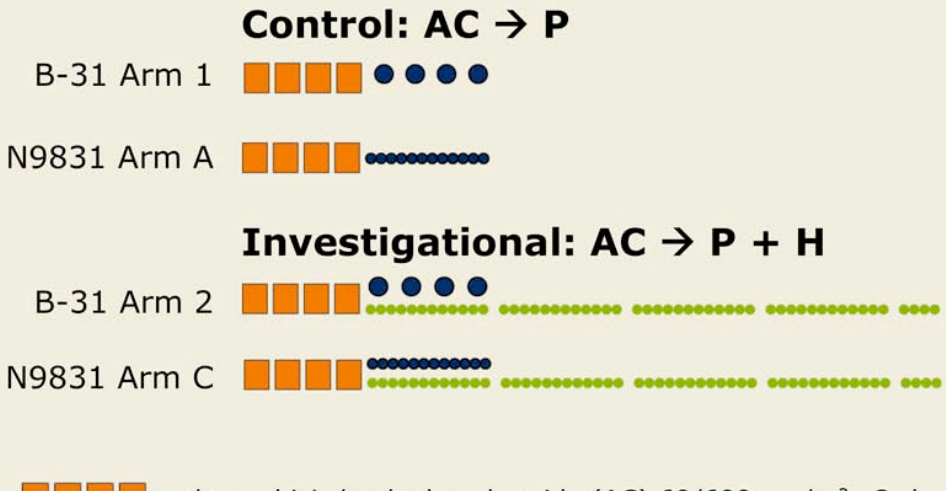
Study Arms in the Combined Analysis of NSABP-B-31 and NCCTG-N9831



= doxorubicin/cyclophosphamide (AC) 60/600 mg/m^2 q3wk x 4
= paclitaxel (P) 175 mg/m^2 q3wk x 4
= paclitaxel (P) 80 mg/m^2 qwk x 12
= trastuzumab (H) 4 mg/kg LD + 2 mg/kg qwk x 51

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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N9831/B-31 Disease-Free Survival

DFS	AC → P + H (n = 2,028)	AC → P (n = 2,018)
10-year DFS*	73.7%	62.2%
First DFS events		
Distant recurrence	11.2%	19.4%
Local/regional recurrence	4.1%	6.1%
Contralateral breast cancer	2.3%	2.0%
Other second primary cancer	3.3%	3.7%
Death without recurrence	1.9%	1.5%

* Adjusted HR = 0.6, $p < 0.0001$

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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N9831/B-31 Cumulative Incidence of Distant Recurrence as a First Event

- ER- and/or PR-positive
  - AC → paclitaxel + trastuzumab: 12.7%
  - AC → paclitaxel: 22.3%
  - Absolute reduction with the addition of trastuzumab: 9.6% at 10 years
- ER- and PR-negative
  - AC → paclitaxel with trastuzumab: 11.9%
  - AC → paclitaxel: 21.5%
  - Absolute reduction with the addition of trastuzumab: 9.6% at 7 years

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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N9831/B-31 Overall Survival

OS	AC → P+H (n = 2,028)	AC → P (n = 2,018)
10-year OS*	84.0%	75.2%
OS events		
Deaths	14.1%	20.7%
Due to this breast cancer	10.3%	16.8%
Due to second primary cancer	1.2%	2.0%
Due to other causes	0.9%	0.7%
Cause unknown	1.6%	1.1%

* Adjusted HR = 0.63, $p < 0.0001$

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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Author Conclusions

- At a median follow-up of 8.4 years, the addition of trastuzumab to AC → P is associated with a significant and substantial improvement in OS, with a relative risk reduction of 37% (HR 0.63).
- For patients with high-risk HER2-positive breast cancer, treatment with this regimen reduces the risk of a DFS event at 10 years by 40% (HR 0.60).
- The relative risk reduction benefit for both DFS and OS was present and of similar magnitude in virtually all subsets of patients analyzed (data not shown).

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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Author Conclusions (Continued)

- For patients with hormone receptor-positive disease, the absolute reduction in the rate of distant recurrence as a first event continues to improve over time with the addition of trastuzumab and reaches 9.6% at 10 years.
- For patients with hormone receptor-negative disease, the absolute risk of distant recurrence as a first event is reduced by 9.6% at 7 years, after which distant recurrence from breast cancer is unlikely.

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

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Investigator Commentary: Trastuzumab with Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Final Planned Joint Analysis of OS from NSABP-B-31 and NCCTG-N9831

The final joint analysis of the NCCTG-N9831 and NSABP-B-31 trials reported survival data after a long-term follow-up of 10 years. The data were fascinating in that they clearly demonstrated that adding trastuzumab to concurrent chemotherapy significantly improves DFS and OS for patients and that this improvement in survival is maintained for a long time. We believe that the data support the concept that many patients who present with HER2-positive breast cancer may be cured with combination strategies. Treatment included anthracycline-based therapy with a taxane and demonstrated no cause for major concern in terms of late toxicities. We are greatly encouraged by the results from this study.

The next question for adjuvant trastuzumab remains whether we can add other agents besides trastuzumab to improve outcomes, because we're still not curing every patient. We've made significant improvements in patient outcomes, but we can do better.

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

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