



**NCCTG-N9831: Adjuvant
Chemotherapy Alone or with
Sequential or Concurrent Addition
of 52 Weeks of Trastuzumab in
HER2-Positive 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. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. 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 meeting, including 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 breast cancer.

LEARNING OBJECTIVE

- Formulate an evidence-based algorithm incorporating trastuzumab for the adjuvant treatment of early, HER2-positive breast cancer.

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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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IN THIS ISSUE:

The long awaited and maybe not so satisfying [third analysis of BCIRG trial 006](#) (TCH versus AC->TH versus AC->T)

- [NCCTG trial 9831](#) data again suggests an advantage to combining chemotherapy and trastuzumab as opposed to sequencing
- Another happy chapter in the rapidly evolving [T-DM1 story](#) with more data demonstrating surprising efficacy in far advanced disease

As Dennis Slamon concluded his [BCIRG 006 presentation](#) in San Antonio last month, I wondered if years from now that moment would symbolize in my mind the end of interest in clinical research on cytotoxic chemotherapy. A generation or more of oncologists have seen the promise and disappointment of these difficult agents, and trials like 006 have sparked endless discussion about which chemo is optimal, a topic that used to permeate all of oncology clinical research.

Since presenting the first “TCH” data set at the 2005 San Antonio meeting, Dr Slamon and others have debated the merits and downsides of anthracyclines in patients with HER2-positive tumors, and a corollary chemo presentation in San Antonio by Dr Edith Perez of [NCCTG trial 9831](#) provided more evidence of the value of combining cytotoxics and trastuzumab as opposed to sequencing with chemo followed by T à la the HERA trial.

The question is: “Who cares anymore?”

In a commentary that accompanies our slide sets this week, Dr Mark Pegram makes the compelling argument that it’s pretty much time to move on from these Talmudic debates on the unknowable, like whether TCH is a better option than AC->TH, and perhaps focus more energy on enrolling patients in studies of new anti-HER2 therapies, like the pretty unusual [T-DM1](#) molecule, which once again in San Antonio put forth unprecedented efficacy numbers in patients with multiple prior anti-HER2 treatments. One might argue that the tiny dollop of maytansine delivered by trastuzumab in T-DM1 is in fact chemotherapy but without alopecia, GI toxicity and myelosuppression.

Everyone in oncology, along with thousands of anxious women who have received adjuvant therapy for HER2-positive breast cancer, have their fingers crossed that we can quickly assess the optimal role of T-DM1 — and for that matter the antibody

pertuzumab and TKIs like lapatinib and neratinib — and have available a new level of treatment efficacy. Hopefully research advances will accelerate in a similar manner for the other 80 percent of patients with HER2-negative tumors.

Next up on 5-Minute Journal Club: “Practice-changing” data on the estrogen receptor downregulator fulvestrant.

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NCCTG-N9831: Adjuvant Chemotherapy Alone or with Sequential or Concurrent Addition of 52 Weeks of Trastuzumab in HER2-Positive Breast Cancer

Presentation discussed in this issue

Perez EA et al. **Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial.** SABCS 2009; [Abstract 80](#).

Slides from a presentation at SABCS 2009 and transcribed comments from an interview with Mark D Pegram, MD (12/23/09)

Results of Chemotherapy Alone, with Sequential or Concurrent Addition of 52 Weeks of Trastuzumab in the NCCTG N9831 HER2-Positive Adjuvant Breast Cancer Trial

Perez EA et al.
SABCS 2009;Abstract 80.

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NCCTG N9831: Trial Schema

Accrual: 3,505 (Closed)

Eligibility

**Resected, Stages I-III
invasive breast cancer**

**HER2-positive, based on
central HER2 testing**



Control Arm

AC q3w x 4 →
T qw x 12

Sequential Arm

AC q3w x 4 →
T qw x 12 →
H qw x 52

Concurrent Arm

AC q3w x 4 →
T + H qw x 12 →
H qw x 40

AC = doxorubicin 60 mg/m²/cyclophosphamide
600 mg/m²

T = paclitaxel 80 mg/m²

H = trastuzumab 4 mg/kg loading dose,
followed by 2 mg/kg

q3w = every three weeks, qw = weekly

Source: Perez EA et al. SABCS 2009;Abstract 80.

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Introduction

- 2000 → NCCTG N9831 study is activated.
 - Objective is to assess the efficacy and cardiotoxicity of chemotherapy administered concurrently or sequentially with trastuzumab (H) in patients with HER2+ breast cancer (BC).
- 2005 → N9831 and NSABP-B-31 joint data published establishing H as standard treatment for patients with HER2+ early stage BC (*NEJM* 2005;353:1673).
- 2008 → Three-year cumulative incidence of NYHA class III or IV congestive heart failure or sudden cardiac death is published (*JCO* 2008;26:1231):
 - 0.3% control arm, 2.8% sequential arm, 3.3% concurrent arm
- 2009 → Efficacy comparisons between the sequential and concurrent study arms are reported.

Source: Perez EA et al. SABCS 2009;Abstract 80.

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Disease-Free Survival (median follow-up > 5 years)

	AC → T	AC → T → H	p-value
Disease free survival rate ¹	71.9%	80.1%	0.0005
Pairwise Comparison	Number of events	Adjusted hazard ratio	p-value
AC → T (n=1,087)	222	0.67	<0.0001
AC → T → H (n=1,097)	164		

¹Second interim analysis.

	AC → T → H	AC → T+H → H	p-value
Disease free survival rate ²	79.8%	84.2%	0.0190 ³
Pairwise Comparison	Number of events	Adjusted hazard ratio	p-value
AC → T → H (n=954)	174	0.75	0.0134 ³
AC → T+H → H (n=949)	138		

²First interim analysis, sequential arm censored during concurrent arm closure;

³Statistical significance preset at 0.00116.

Source: Perez EA et al. SABCS 2009;Abstract 701.

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Overall Survival (median follow-up > 5 years)

Pairwise Comparison	Number of events	Unadjusted hazard ratio	p-value
AC → T vs AC → T → H (n=2,184)	220	0.86	0.281
AC → T → H vs AC → T+H → H (n=1,903)*	168	0.79	0.135

*Patients on the sequential arm were excluded when the concurrent arm was closed.

Source: Perez EA et al. SABCS 2009;Abstract 701.

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Conclusions

- DFS is significantly improved with the addition of 52 weeks of trastuzumab to AC → T.
 - 5-year DFS: 72% (control) vs 80% (sequential) vs 84% (concurrent)
- The risk of an event is significantly reduced by 33 percent by sequential addition of trastuzumab to chemotherapy.
 - Number of events: 222 (control) vs 164 (sequential)
- A strong trend exists for a 25 percent reduction in the risk of an event when trastuzumab is administered concurrently with taxane chemotherapy relative to sequentially.
- Adjuvant trastuzumab should be incorporated in a concurrent fashion with the taxane portion of chemotherapy (AC → T + H → H).

Source: Perez EA et al. SABCS 2009; Abstract 80.

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DR PEGRAM: I found this presentation intriguing. When I was working in Dennis Slamon's laboratory at UCLA, we published a series of papers showing that the combination of cytotoxic agents with trastuzumab was superior in cell-based assays and in xenografts than when given in sequence.

Moreover, if you gave the agents in sequence deliberately in an experimental model, both in vitro and in vivo, it was always better to give the trastuzumab first followed by the cytotoxic agent and not the other way around. When we did the original drug development strategy for trastuzumab, we deliberately integrated it in combination with cytotoxics in an effort to exploit any potential synergy between the two. The Perez trial addressed this question clinically in a large adjuvant study that compared the sequence of chemotherapy followed by trastuzumab to AC followed by paclitaxel given in combination with trastuzumab followed by a total of a year of adjuvant trastuzumab.

The study design was nice because it allowed for the first time in the adjuvant setting a head-on comparison of the schedules of trastuzumab — whether it is best to use in sequence or in combination. The European adjuvant trastuzumab trial was all done as a sequence, in which generally chemotherapy was followed by trastuzumab. The common practice outside of North America is to use sequence rather than combination.

Just as they had shown a few years ago in an unplanned interim analysis, these most recent updated data from Dr Perez also showed superiority of the combination over the sequence. The data looked fairly convincing and conclusive until you examined the statistical plan of the protocol. The O'Brien-Fleming p -value that must be achieved in order to call this statistically significant in the preplanned analysis was 0.001. The actual p -value was 0.019. If you're a purist, you could argue that this did not cross the boundary for statistical significance, even though it looks compelling that the combination is better than the sequence.

This is a little bit of an unsatisfying result. It fits my preconceived notion and my clear bias that the combination is probably better, but there's this nagging issue that it doesn't quite hit the mark in terms of the preplanned p -value. It is a nonsignificant trend, but it seems to be a trend of a significant enough magnitude to possibly merit clinical consideration.

Clinicians can digest the data as they see fit. The overarching question is whether or not to use the trastuzumab, and that has been definitively answered. Which chemotherapy or whether you use the sequence or the combination are relatively trivial considerations compared to the magnitude of benefit that we see by simply administering some trastuzumab in any way, shape or form.

Dr Pegram is Full Professor of Medicine and Director for the Translational Research Program at the UM Sylvester Comprehensive Cancer Center's Braman Family Breast Cancer Research Institute in Miami, Florida.