5 Minute JournalClub

Efficacy of Trastuzumab-Based Regimens in Patients with HER2-Amplified Early-Stage 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

- Identify the clinical efficacy and toxicity associated with the AC → T, AC → TH and TCH regimens when administered to patients with HER2-amplified early-stage breast cancer.

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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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Efficacy of Trastuzumab-Based Regimens in Patients with HER2-Amplified Early-Stage Breast Cancer

Presentation discussed in this issue

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients: BCIRG 006 study.** SABCS 2009;**Abstract 62**.

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

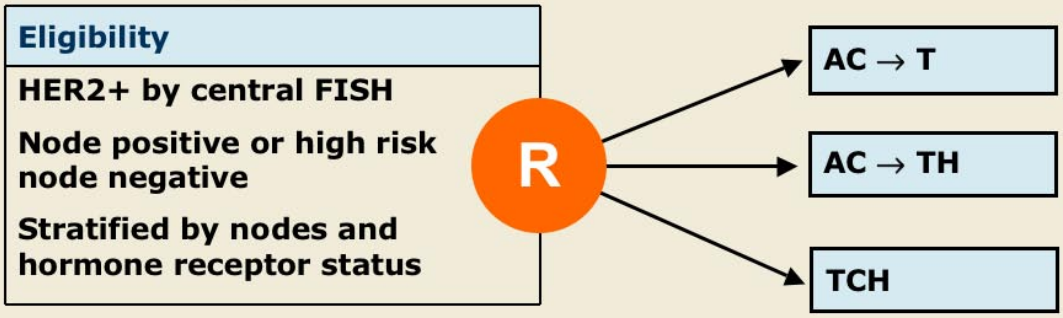
Introduction

- Trastuzumab treatment is associated with cardiac dysfunction, especially in patients who have received anthracyclines.
- Pre-clinical data suggested that there is a synergy between trastuzumab and docetaxel/carboplatin that is not seen with anthracyclines.
- **Current study objectives:**
  - Assess the efficacy, safety and cardiac safety of an anthracycline regimen compared to the same regimen with trastuzumab (H) versus a nonanthracycline regimen with H in patients with HER2-amplified early breast cancer.

Source: Slamon D et al. SABCS 2009;Abstract 62.

BCIRG 006: Study Design

Accrual: 3,222 (Closed)



AC → T = *AC (Adriamycin 60 mg/m², Cyclophosphamide 600 mg/m²) q 3 weeks x 4 followed by T (Docetaxel 100 mg/m²) q 3 weeks x 4*

AC → TH = *AC (Adriamycin 60 mg/m², Cyclophosphamide 600 mg/m²) q 3 weeks x 4 followed by T 100 mg/m² q 3 weeks x 4. Trastuzumab (H) initiated with T x 1 year*

TCH = *T (75 mg/m²) and Carboplatin (AUC 6) q 3 weeks x 6. H initiated with TC x 1 year*

Source: Slamon D et al. SABCS 2009;Abstract 62.

BCIRG 006: Tumor Characteristics

	AC → T n = 1073 %	AC → TH n = 1074 %	TCH n = 1075 %
Number of Nodes (+)			
0	29	29	29
1-3	38	38	39
4-10	22	24	23
> 10	11	9	10
Tumor Size (cm)			
≤ 2	41	38	40
> 2 and ≤ 5	53	55	54
> 5	6	7	6
ER and/or PR (+)	54	54	54

Source: Slamon D et al. SABCS 2009;Abstract 62.

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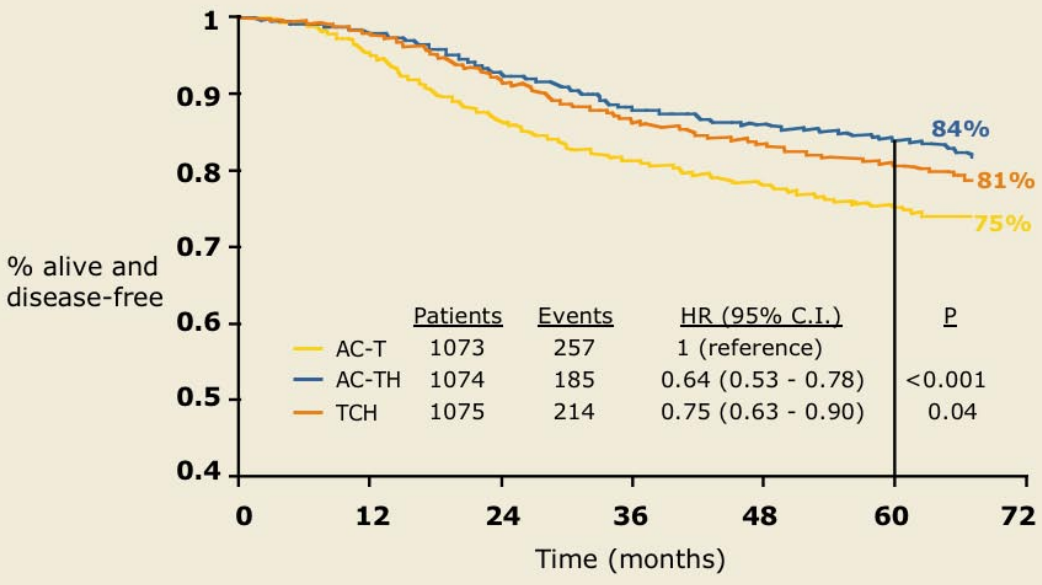
Disease Free Survival (DFS) 3rd Planned Analysis (median follow-up 65 mos)



Source: With permission Slamon D et al. SABCS 2009;Abstract 62.

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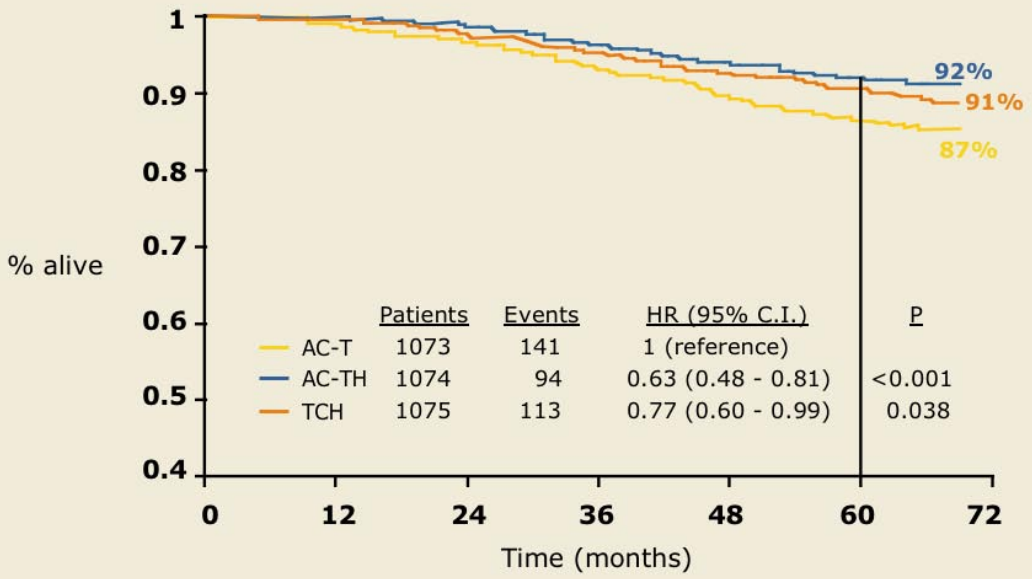
Overall Survival
3rd Planned Analysis
(median follow-up 65 mos)



Source: With permission Slamon D et al. SABCS 2009;Abstract 62.

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DFS According to Nodal and Topo IIa Amplification Status

Lymph Node Status	AC → T	AC → TH	TCH
Lymph node negative (n=309, 310, 309)	85%	93%	90%
Lymph node positive (n=764, 764, 766)	71%	80%	78%
Lymph nodes ≥ 4 (n=350, 350, 352)	61%	73%	72%
Topo IIa Amplification			
Topo IIa non co-amplified (n=643, 643, 618)	**70%**	83%	80%
Topo IIa co-amplified (n=328, 357, 359)	**83%**	85%	82%

Source: Slamon D et al. SABCS 2009;Abstract 62.

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Safety Endpoints

- No cardiac related deaths were observed in any of the three study arms.
- Grade 3/4 CHF was lower in the TCH arm.
  - 0.4% with TCH versus 0.7% with AC → T versus 2% with AC → TH.
- The incidence of >10% decline in LVEF was lower in the TCH arm.
  - 9% with TCH versus 19% with AC → TH versus 11% with AC → T
- Eight patients in BCIRG 006 have developed acute leukemias to date.
  - Six cases in AC → T, one case in AC → TH and one case in TCH (patient received CHOP for subsequent diagnosis of lymphoma prior to acute leukemia development)

Source: Slamon D et al. SABCS 2009;Abstract 62.

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BCIRG 006: Therapeutic Index

	AC → TH n = 1074	TCH n = 1075
DFS Events	185	214
Grade 3 / 4 CHF	21	4
Totals	206	218
Treatment-related leukemias	1	1*
Sustained LVEF loss > 10%	194	97

* Leukemia developed after CHOP chemotherapy

Source: Slamon D et al. SABCS 2009;Abstract 62.

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Conclusions: BCIRG 006

- Trastuzumab provides a similar and significant advantage for both DFS and OS in low- and high-risk patients when used either as AC → TH or as TCH.
- Acute and chronic toxicity profiles of TCH are better than AC → TH.
- Though there is no statistical advantage, the AC → TH arm had a 29 event numerical advantage in DFS events over that of the TCH arm.
  - Numerical advantage, however, was associated with 5 times more cases of CHF in the AC → TH arm than in the TCH arm.
- All three regimens showed similar efficacy in a subset of patients with Topo IIa co-amplification.
  - The incremental benefit of AC that is known for HER2+ BC appears restricted to TOPO IIa co-amplified cancers.

Source: Slamon D et al. SABCS 2009;Abstract 62.

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DR PEGRAM: This was the third planned interim analysis of the BCIRG 006 trial. It is important to note that the study was not powered to compare TCH to AC → TH. Any comparison between the two trastuzumab arms that one makes in this trial is unplanned and speculative.

There were two prior planned interim analyses that had been presented that demonstrated that both of the trastuzumab-containing arms were significantly superior to the nontrastuzumab control, which was anthracycline and taxane-based combination chemotherapy.

It appeared previously that there might have been a graphical trend in favor of the AC → TH arm compared to the TCH arm. However, when statistical tests have been applied comparing the two trastuzumab-containing arms, there is no statistical difference in the first two interim analyses. In this third planned interim analysis, there is again the graphical appearance that the anthracycline-containing arm is trending a little bit better. From a statistical point of view it is again impossible to discriminate fairly between the two trastuzumab-containing arms. Since the study was not powered for noninferiority, one cannot rule out the possibility that anthracycline-containing regimens might be slightly better. The absolute numbers of adverse events and deaths between the arms suggest that there could be some trends in favor of anthracyclines.

The BCIRG group made the supposition that anthracyclines would be more important in patients with lots of positive nodes, as opposed to those with node-negative disease. They performed that comparison and found that there was no difference in the group of patients with lots of nodes with regard to efficacy of AC → TH versus TCH. The notion that intrinsic risk might be a clinical factor that one could use to decide whether to use anthracyclines did not hold up.

DR LOVE: In general, have you been using TCH yourself off study?

DR PEGRAM: I have been. It is an efficacious regimen that does have a different spectrum of toxicities, and therefore it is a therapeutic consideration. If somebody came to me for a second opinion and the referring physician had recommended an AC followed by TH approach, I would not say that it was inappropriate. It might be entirely appropriate. But I would argue that it's reasonable for patients to understand that both of these are treatment options that are available to them, and they can weigh in based on their understanding of the various toxicities.

DR LOVE: Are you generally continuing to use TCH as your preferred regimen?

DR PEGRAM: I am generally continuing to use TCH as my preferred regimen. TCH is a reasonable treatment option, but clearly there is this non-statistically significant trend in favor of the AC → TH arm. It suggests the possibility that there could be inferiority of TCH in an appropriately powered study, which has not been conducted. It remains an open question.

In the grand scheme of things, I believe history will record that quibbling over which chemotherapy backbone to use with trastuzumab is going to be irrelevant. We need to move on and the next question is: Can we do better than chemo/trastuzumab?

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.