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

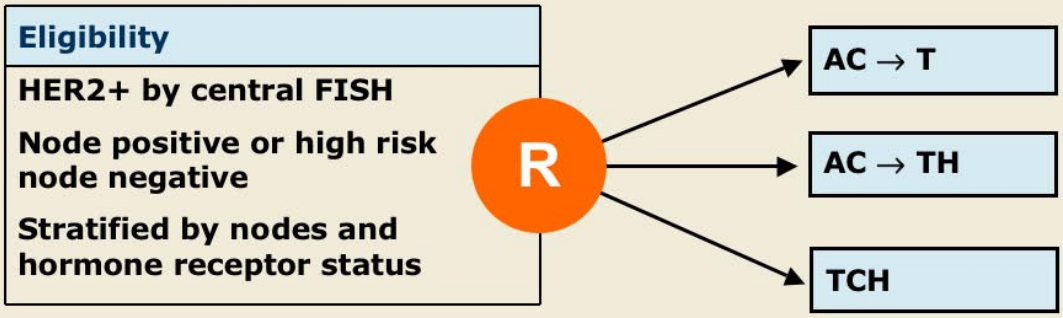
Introduction

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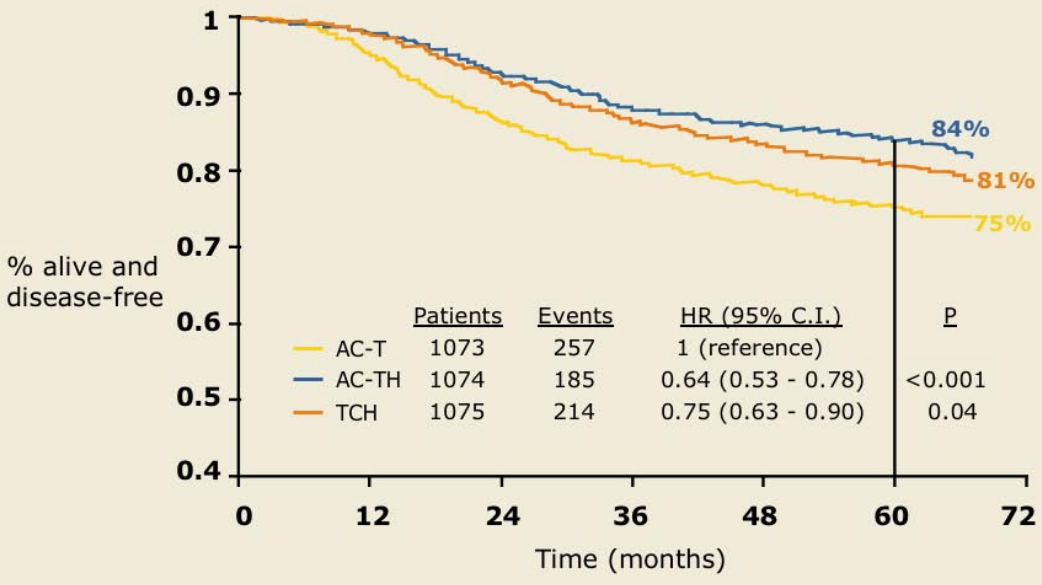
Disease Free Survival (DFS) 3rd Planned Analysis (median follow-up 65 mos)



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

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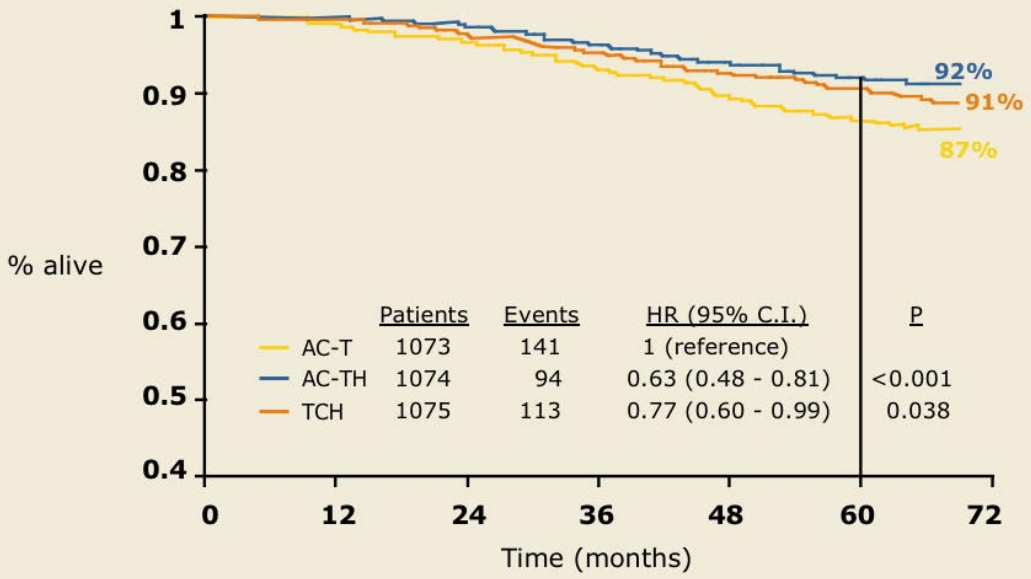
Overall Survival
3rd Planned Analysis
(median follow-up 65 mos)



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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