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Concurrent trastuzumab and paclitaxel treatment improves disease-free survival in resected HER2-positive breast cancer: NCCTG N9831 interim analysis

E. Perez[1], V.J. Suman[2], N. Davidson[3], S. Martino[4], P. Kaufman[5]. [1]*Mayo Clinic, Dept of Haematology/Oncology, Jacksonville, USA;* [2]*Mayo Clinic, Dept of Biostatistics, Rochester, USA;* [3]*Johns Hopkins University, Johns Hopkins Oncology Center, Baltimore, USA;* [4]*John Wayne Cancer Institute, St. Johns Health Center, Santa Monica, USA;* [5]*Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, USA*

Background: The NCCTG N9831 study was devised to evaluate whether 1 year of trastuzumab (Herceptin® H) adds to the benefit of adjuvant doxorubicin/cyclophosphamide chemotherapy (AC) followed by paclitaxel (T) treatment in resected HER2-positive breast cancer. The study also evaluated the impact of trastuzumab (H) when given concurrently or sequentially as well as verifying cardiac safety.
Methods: Eligibility criteria included resected invasive breast cancer, node positive or high-risk node negative tumour (>1.0 cm if ER− or >2.0 cm if ER+), HER2 positive status verified by central testing (IHC 3+ or FISH+), normal left ventricular ejection fraction (LVEF) and no prior myocardial infarction or congestive heart failure. Clinical endpoints were disease-free survival (DFS; primary) and overall survival (OS). A total of 3,505 patients were randomised to three treatment arms: A (control, AC → T), B (sequential, AC → T → H), and C (concurrent, AC → TH → H). Pairwise comparisons were planned: A versus B, A versus C, and A plus B versus C. LVEF changes were reviewed monthly. Patients randomised to sequential or concurrent H treatment were only given H if normal LVEF was maintained or it did not drop by >15% from baseline after AC.
Results: Results of the joint analysis of this study and NSABP-B31 showed that treatment arm C (concurrent H with T) significantly improved DFS by 52% and OS by 33% versus A ($p = 3 \times 10^{-12}$), prompting an unplanned interim analysis looking at the timing of incorporating H treatment. At this time, there were 220 DFS events available for comparisons between A and B and 147 events for B and C. Treatment arm B improved DFS by 13% versus A ($p = 0.2936$); C improved DFS by 36% versus B ($p = 0.0114$). At month 9, there were no cardiac events (CHF and cardiac death) with arm A, 2.2% with B and 3.3% with C. The difference in the incidence of cardiac events between non-H and H arms was <4%. Updated information on cardiac safety will be available in the Fall of 2005.
Conclusions: H significantly improves DFS in resected HER2-positive breast cancer when given concurrently with T after AC. Concurrent therapy leads to better DFS compared to sequential therapy, but more follow up is needed to reach definite conclusions regarding the best time to incorporate H with chemotherapy. Exploration of predictive factors for cardiac safety is ongoing. Further interim analyses are planned.

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BCIRG 006: Superior cardiac safety of adjuvant docetaxel (T), carboplatin (C) and trastuzumab (H) compared to doxorubicin (A) and cyclophosphamide (Cyc) followed by TH in patients with early stage breast cancer and altered HER2 gene.

D. Slamon[1], W. Eiermann[2], N. Robert[3], T. Pienkowski[4], M. Martin[5], M. Pawlicki[6], M. Chan[7], M. Buyse[8], V. Bee[9], J. Crown[10]. [1]*UCLA Jonsson Comprehensive Centre, Oncology, California, USA;* [2]*GABG, Oncology, Munchen, Germany;* [3]*US Oncology, Oncology, Dallas, USA;* [4]*The Maria Sklodowska-Curie Memorial Cancer Centre, Oncology, Warsaw, Poland;* [5]*GEICAM, Oncology, Madrid, Spain;* [6]*Maria Sklodowska-Curie Memorial Cancer Institute, Oncology, Krakow, Poland;* [7]*Mount Hospital, Oncology, Perth, Australia;* [8]*IDDI, Statistics, Brussels, Belgium;* [9]*CIRG, Oncology, Paris, France;* [10]*St. Vincent's University Hospital, Medical Oncology Research Department, Dublin, Ireland*

Background: Pts with altered HER2 gene (HER2+) early stage breast cancer (ESBC) have a poor prognosis. H is active in pts with HER2+ metastatic (M) BC, mandating adjuvant study in ESBC. The BCIRG 006 study uses a novel translational-derived H-containing adjuvant regimen based on preclinical studies indicating synergy between H and both T and C, respectively, but not with A. The cardiotoxicity noted when H is given to pts with anthracycline exposure provided an additional rationale for a non-classical non-anthracycline design. Pending the accrual of sufficient relapses to activate statistical analysis for efficacy (due autumn 2005), we now present the data for cardiac toxicity.
Methods: As required by protocol, all women randomized had normal ejection fraction (EF) at baseline. EF was repeated at 3, 4.5, 6, 9 and 18 months. Interim cardiac analyses were planned after 100, 300, 500 patients in each arm had been followed for at least 9 months. Presented here are the results from all patients randomized having received at least one cycle of treatment. The cardiac endpoint was cardiac events (cardiac death, grade 3/4 left ventricular function (CHF), grade 3/4 arrhythmia or grade 3/4 ischemia/infarction). An absolute difference of 4% would trigger suspension of the H arm(s).
Results: A total of 3171 patients were evaluated, with a median follow-up of 17.6 months. The protocol-defined stopping rules were not met and recruitment was completed as planned. There were 53 cardiac events: ACyc-T 12 (1.2%), ACyc-TH 28 (2.3%) and TCH 13 (1.2%) [Fisher's exact test: ACyc-T vs ACyc-TH, $p = 0.046$; ACyc-T vs TCH, $p = 1.00$)]. There were no cardiac deaths. Clinical CHF occurred in 20 patients (ACyc-TH 18 patients, ACyc-T and TCH with 1 each). Absolute LVEF decline >15% occurred in 6 patients in ACyc-T, 25 in ACyc-TH and 4 in TCH arm with ACyc-T vs ACyc-TH reaching statistical significance ($p = 0.001$) and ACyc-T vs TCH not showing a significant difference ($p = 0.54$). A mixed model analysis of EF decline over time revealed statistically significant declines for ACyc-T and ACyc-TH, but not for TCH.
Conclusions: 1) The translational-derived regimen TCH is significantly less cardiotoxic than the empirically-derived ACyc-TH regimen. 2) H does not appear to contribute significant cardiotoxicity in non-anthracycline-based regimens. These data will be subjected to external review.

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NCIC CTG MA17: Increasing benefit of letrozole with longer duration of treatment as measured by the hazard ratio of disease recurrence over time

J. Ingle[1], P. Goss[2], T. Dongsheng[3]. [1]*Mayo Clinic, Oncology, Rochester, USA;* [2]*Massachusetts General, Hematology/Oncology, Boston, USA;* [3]*On behalf of the MA.17 Collaborative Trialists. 3NCIC CTG, Oncology, Worldwide*

Background: MA 17 randomized 5187 postmenopausal women with early stage breast cancer after 5 years of tamoxifen to 5 years of letrozole (L) or placebo (P). After 30 months median follow-up (range 1.5–61.4 months), disease-free survival (DFS) was superior in the overall study population for L (HR 0.58 with 95%CI 0.45–0.76; $p = 0.00004$).
Materials and Methods: A nonparametric kernel method was used to estimate the hazard rates and hazard ratio, as a measure of treatment effect, at various time points. A Cox model with a time-dependent covariate was used to test the trend of the hazard ratio over time.
Results: For placebo patients, there was an increasing risk of disease recurrence over time after discontinuing prior tamoxifen. For letrozole patients, the risk of recurrence peaked at two years of treatment and decreased thereafter. A comparison of the placebo versus letrozole group, showed a statistically significant trend to a decreasing hazard ratio indicating greater benefit of letrozole over time ($p = 0.02$).

Month after randomization	Number at risk (L/P)	Hazard rate (L)		Hazard ratio (L vs P)*
		(L)	(P)	
12	2425/2409	0.00093	0.00180	0.52 (0.40–0.64)
24	1555/1530	0.00105	0.00236	0.45 (0.33–0.56)
36	768/723	0.00090	0.00261	0.35 (0.21–0.48)
48	244/231	0.00059	0.00306	0.19 (0.04, 0.34)

*Hazard ratios less than one indicate values in favor of letrozole.

Conclusions: MA.17 demonstrated a highly significant improvement in DFS at the first interim analysis. Consequently the trial was stopped early and the optimal duration of therapy left uncertain. This analysis of the diverging hazard ratios over time between the letrozole and placebo arms of the trial implies that the longer patients are exposed to letrozole the greater the benefit. A re-randomization (MA.17R) to a further five years of letrozole versus placebo in women completing 5 years of letrozole in the core MA.17 trial is now actively accruing in order to gain more information on the optimal duration of letrozole adjuvant therapy in women with early-stage breast cancer.

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Oral NCIC CTG MA17: Disease free survival according to estrogen receptor and progesterone receptor status of the primary tumor

P. Goss[1], J. Ingle[2], T. Dongsheng. *On behalf of the MA.17 Collaborative Trialists (NCIC CTG, Oncology, Worldwide).* [1]*Massachusetts General Hospital Cancer Center, Hematology-Oncology, Boston, USA;* [2]*Mayo Clinic, Oncology, Rochester, USA*

Background: MA.17 randomized 5187 postmenopausal women with early breast cancer who were free of disease after 5 years of tamoxifen to 5 years of letrozole or placebo. After 30 months median follow-up (range