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

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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.

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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

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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

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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

1.5–61.4 months), the hazard ratio (HR) for DFS in the overall population was 0.58 (0.45–0.76, p = 0.00004) in favor of letrozole. Almost all patients (97.4%) had estrogen receptor (ER) and/or progesterone receptor (PgR) positive primary tumors.
Materials and Methods: Both ER and PgR values were known in 4653 patients and retrospective exploratory analyses were conducted to compare time to recurrence in the four receptor sub-groups by ER (±) and PgR (±) status. ER and PgR positivity was defined as ⩾10 fmol/mg protein, or positive by ERICA or PgRICA.
Results: The results are shown below. As indicated the benefit of letrozole was most pronounced in women with ER+PgR+ and ER-PgR+ tumors. The ER+PgR+ compared with the ER+PgR− group indicated a statistically significant difference in the treatment effect between them (p = 0.02) however this was not a pre-planned comparison. Adjustment for nodal status and prior adjuvant chemotherapy did not affect this result.

	n	Letrozole (L) events	Placebo (P) events	HR* L vs P (95%CI)
ER+ PgR+	3809	60 (3%)	117 (6%)	0.50 (0.36–0.68)
ER+ PgR−	636	19 (6%)	17 (5%)	1.19 (0.62–2.29)
ER7minus; PgR+	200	4 (4%)	5 (5%)	0.62 (0.17–2.31)
ER− PgR−	8	–	–	–

*Hazard ratios for event in DFS (HR less than one indicates value in favor of letrozole)

Conclusions: The effect of letrozole in this placebo-controlled trial appears most pronounced in women with the most hormone dependent, ER+ PgR+, tumors. Its apparent benefit in ER− PgR+ve tumors and lack thereof in ER+ PgR− implies activity of letrozole against disease with a functional ER. The results presented here should be interpreted with caution as it was an unplanned analysis, there is overlap between the HR's and the receptor levels were measured locally. A plan for central measurement and comparison of standard ER and PgR levels is now underway.

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Gynaecological adverse events and hysterectomies in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial

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Background: The Completed Treatment Analysis of the ATAC trial at a median follow-up of 68 months showed that anastrozole is a more effective and better tolerated treatment than tamoxifen as primary adjuvant treatment for postmenopausal women (n = 9366) with hormone-sensitive early breast cancer (EBC). Treatment with anastrozole was associated with significant reductions in the incidence of predefined gynaecological adverse events (AEs) compared with tamoxifen: vaginal bleeding 5.4% vs 10.2%, p < 0.0001; vaginal discharge 3.5% vs 13.2%, p < 0.0001; endometrial cancer 0.2% vs 0.8%, p = 0.02.
Methods: This retrospective analysis investigated all gynaecological AEs and hysterectomies recorded on the ATAC main trial database.

Diagnoses leading to hysterectomy in the ATAC trial

	Anastrozole (n = 2228)[a] n (%)	Tamoxifen (n = 2236)[a] n (%)
Hysterectomy all diagnoses	30 (1.3)	115 (5.1)
Malignancy	7 (0.3)	20 (0.9)
Benign	23 (1.0)	95 (4.2)
Prolapse	7 (0.3)	32 (1.4)
Fibroids	8 (0.4)	15 (0.7)
Polyps	1 (< 0.1)	14 (0.6)
Ovarian cysts	2 (0.1)	4 (0.2)
Other	5 (0.2)	30 (1.3)

[a]Patients with an intact uterus at baseline

Results: Overall, gynaecological AEs were significantly less common with anastrozole compared with tamoxifen (20.5% vs 34.2%, p < 0.0001). This difference was largely accounted for by lower incidences of endometrial hyperplasia (0.7% vs 6.1%*), endometrial neoplasia (1.0% vs 5.3%*), leucorrhoea (2.7% vs 9.2%), and vaginal haemorrhage (5.2% vs 8.3%*) with anastrozole compared with tamoxifen [*Percentages derived from patients with an intact uterus at baseline]. Treatment with anastrozole was also associated with an almost four-fold reduction in the incidence of hysterectomy due to both malignant and benign diagnoses in women with an intact uterus at baseline (Table). The majority of gynaecological AEs occurred during the first 2.5 years of treatment.
Conclusions: Not only is treatment with anastrozole associated with a significantly lower risk of gynaecological AEs compared with tamoxifen but the substantially higher hysterectomy rate in women treated with tamoxifen compared with those treated with anastrozole is a cause for concern. Thus, treatment with anastrozole rather than tamoxifen may avoid the psychological distress and associated costs of investigations and/or treatment for gynaecological side effects for many women. The findings of this analysis further support that anastrozole should now be considered the preferred primary adjuvant treatment for postmenopausal women with EBC.

Oral presentations (Wed, 2 Nov, 9.15–11.15)
Early breast cancer – issues related to locoregional therapy

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Lumpectomy plus tamoxifen or arimidex with or without whole breast irradiation in women with favourable early breast cancer

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Background: In women with favourable early breast cancer treated by lumpectomy plus tamoxifen or arimidex it remains unclear, whether breast irradiation is beneficial with regard to local control, disease-free and overall survival.
Methods: Between 1/1996 and 6/2004, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) randomly assigned 875 women (24 ineligible, 25 excluded: total 826) within the clinical ABCSG trial 8 (Jakesz et al., SABCS 2004) to receive whole breast irradiation ± boost (group I, n = 410) or not (group II, n = 416) (ABCSG study 8A). Favourable early breast cancer was specified as tumour size <3 cm, negative lymph nodes, positive estrogen and/or progesteron receptor status, and manageable by breast conserving surgery. Breast radiotherapy was performed after lumpectomy with two tangential opposed breast fields with 50 Gy plus boost in 66% of patients with 10 Gy, median in 6 weeks.
Primary endpoint was local relapse. Further endpoints were contra-lateral breast cancer, distant metastases, disease-free and overall survival. The median follow-up was 42 months.
Results: Mean age was 66 years (±8). Overall, there were 14 local relapses (1.7%), with 1 local relapse in the irradiated group (I) (0.2%) versus 13 local events in the non-irradiated group (II) (3.1%) (p = 0.001). Contra-lateral breast cancer was 0 versus 4, respectively (p = 0.04). Overall, there were 9 pts. with distant metastases, 5 (1.2%) versus 4 (0.96%) in group I and II, respectively (p = 0.76). Overall recurrence was in 46 pts. with 18 events (4.4%) in group I versus 28 events (6.7%) in group II (p = 0.12). Overall survival was 97.2% (23 events) with 97.8% (9 events) in group I versus 96.6% (14 events) in group II (p = 0.28).
Conclusion: Whole breast radiotherapy ± boost in women with favourable early breast cancer after lumpectomy combined with tamoxifen/arimidex leads to a significant reduction in local relapse and contra-lateral breast cancer. After a median follow-up of 42 months, there is no significant impact on distant metastases, disease free and overall survival.