Conclusion: the novel NNBC-3 risk algorithm classifies considerably more patients to the low-risk group than Adjuvant! or the St. Gallen 2007 risk category and is the only risk classification predicting DFS as well as OS in multivariate analysis.

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Dutch population-based validation of the prognostic evaluation tool Adjuvant!

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Background: Adjuvant treatment recommendations for early stage breast cancer depend on the risk of disease recurrence and the expected benefit of adjuvant therapy. Adjuvant! is a web-based tool that calculates individualized 10-year survival probability and estimated benefit of adjuvant systemic therapy based on age, co-morbidity, tumour size, grade and oestrogen-receptor status. This model is constructed using 10-year observed overall survival for women diagnosed with breast cancer between 1988 and 1992 recorded in the US SEER registry (Surveillance, Epidemiology and End Results). In 2005, Adjuvant! was validated in 4,083 patients from British Columbia (Olivotto et al. JCO). In the Netherlands, Adjuvant! is used in addition to the national 'CBO' (The Dutch Institute for Healthcare Improvement) guidelines. The aim of our study is to validate the estimated disease outcome by Adjuvant! in a Dutch breast cancer population.

Methods: Clinicopathologic characteristics and treatment data were registered prospectively in the Eindhoven Cancer Registry. There are 16,881 patients in this registry with T1−T3, N1−N3, M0 primary breast cancer diagnosed between 1970 and 2004. For this analysis, we will use those patients for which there are the variables used by Adjuvant!, and we will explore whether systematic biases are introduced in cases with missing data. Patients were between 20 and 90 years of age at diagnosis and were treated with breast conserving therapy or mastectomy with definitive axillary staging. About 40% of the patients received adjuvant systemic therapy. Adjuvant! is used to calculate predicted 10-year breast cancer outcome for each patient, and compared to observed outcomes.

Results: The concordance between predicted and observed survival for the overall cohort and for subgroups of age and years of diagnosis will be presented at the meeting. In addition, a multivariate analysis will be performed to evaluate whether the prognostic features used by Adjuvant! (such as histologic grade) are prognostic in this patient population.

Future prospects: In addition to this Dutch population-based validation of Adjuvant!, we will also validate the tool in two hospital-based patient cohorts from the Netherlands (~10,000 cases). Finally, when Adjuvant! performs reliably in the Dutch breast cancer population, the tool will be considered for the national guidelines for adjuvant treatment-decision. This is the first European large scale validation of Adjuvant!

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The 70-gene profile is a powerful predictor of disease outcome in breast cancer patients with 1−3 positive lymph nodes

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Introduction: The axillary lymph node status is considered to be one of the most powerful prognostic factors for operable breast cancer, with a decrease in survival as the number of positive nodes increases. However, approximately 30% of lymph node-positive patients will remain free of distant metastases without adjuvant chemotherapy. We have previously shown in two independent datasets that the '70-gene profile (MammaPrint®™)', which was developed in node-negative patients (van 't Veer *et al.* Nature 2002), is excellent in predicting disease outcome in patients with 1−3 positive nodes (NEJM 2002; SABCS 2007). We now combine the two datasets to allow further detailed analysis.

Methods: Three-hundred-forty-seven patients with T1, T2 or operable T3 breast cancer and 1−3 positive lymph nodes of 2 hospitals were selected. Patients were treated with breast conserving therapy or mastectomy with axillary lymph node dissection. Thirty-nine patients (11%) received no adjuvant systemic therapy, 118 (34%) chemotherapy only, 94 (27%) endocrine therapy only, and 84 patients (24%) received both. Median follow-up was 8.7 years. Distant metastases occurred in 75 patients. Samples were analyzed by gene expression profiling for the 70-gene profile.

Results: Among the 347 patients, 142 (41%) were assigned to the genomic low risk and 205 (59%) to the genomic high risk group. The 5- and 10-year overall survival (OS) probability was 99% (SE 1%) and 96% (SE 2%) for the genomic low risk group versus 86% (SE 3%) and 68% (4%) for the genomic high risk group, respectively. In a multivariate analysis adjusted for known prognostic factors, the 70-gene profile was a powerful significant predictor of OS and distant metastases as first event, with an estimated hazard ratio (HR) of 4.8 (95% CI 2.0−11.7; $p < 0.001$) and 3.0 (95% CI 1.4−6.7; $p = 0.006$), respectively. The profile maintained its prognostic value for OS (HR 3.9, $p = 0.02$) in a multivariate model including an interaction term between chemotherapy and the profile (interaction $p = 0.60$).

Conclusion: Our data show that the 70-gene profile is a strong predictor of overall survival and distant metastases as first event in patients with 1−3 positive lymph nodes. Furthermore, the profile can accurately identify a group of patients with an excellent survival who may be safely spared chemotherapy. Based on these data the inclusion criteria of the MINDACT trial will be enlarged to include patients with 1−3 positive nodes.

Friday, 18 April 2008 12:30–14:30

POSTER SESSION

Side effects of treatment

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Risk of febrile neutropenia as a function of age and disease stage in breast cancer patients receiving pegfilgrastim primary prophylaxis versus current practice neutropenia management – results from the NeuCuP analysis

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Background: Febrile neutropenia (FN) is a serious adverse event related to myelosuppressive chemotherapy (CT). Age and disease stage also determine overall FN risk. Granulocyte colony-stimulating factor (G-CSF) prophylaxis can reduce the incidence of FN and related complications, but its use in current practice (CP) can be inconsistent. Here, we compare predicted risk of FN for patients in different age groups and stages of breast cancer depending on whether they received pegfilgrastim primary prophylaxis (PPP) or CP neutropenia management.

Methods: Studies involving breast cancer CT regimens with moderately–high (15−20%)/high (≥20%) risk of FN were identified by literature review. For this integrated analysis, individual patient data were available from 8 clinical trials and 3 observational studies involving these regimens and PPP (6 mg, all cycles) or CP (no G-CSF or pegfilgrastim/daily G-CSF in any cycle). The primary outcome measure was the overall incidence of FN. A mixed effects generalized linear model was fitted in which treatment arm (PPP vs CP), age and disease stage (I−III vs IV) influenced FN. The model was used to predict proportions of patients with FN depending on their age and disease stage.

Results: 2282 patients were analyzed: mean age (±SD, yrs) was 51.4±10.4 for PPP vs 52.0±9.9 for CP, 28% vs 28% had Stage IV disease, and 30% vs 37% had prior CT/radiotherapy. The most common regimens were docetaxel (Doc) (37% vs 50%), Doc / doxorubicin(A) / cyclophosphamide (31% vs 27%), and ADoc (27% vs 3%). In cycle 1, 75% of CP patients had no G-CSF. In the model ($N = 2210$), the odds for FN were significantly lower with PPP vs CP (OR: 0.124; 95% CI: 0.08, 0.194; $P < 0.0001$). The predicted proportions of patients with FN ranged from 3% vs 22% (PPP vs CP) for a young patient with early stage disease, to 8% vs 41% in an elderly patient with metastases (Table).

Conclusions: PPP was associated with significantly lower odds of FN than CP in breast cancer patients receiving CT with moderately-high/high FN risk. These data illustrate the likely clinical benefits of PPP over CP in patients of all ages and stages of disease.

Age at baseline (yrs)	Predicted proportion of patients with FN (95% CI)			
	Disease stage I–III at baseline		Disease stage IV at baseline	
	PPP (N = 930)	CP (N = 646)	PPP (N = 361)	CP (N = 273)
40	3% (2%, 6%)	22% (12%, 36%)	5% (2%, 9%)	28% (16%, 45%)
50	4% (2%, 8%)	25% (15%, 40%)	6% (3%, 11%)	32% (19%, 49%)
60	5% (3%, 9%)	29% (17%, 45%)	7% (3%, 13%)	37% (22%, 54%)
70	6% (3%, 11%)	33% (20%, 50%)	8% (4%, 15%)	41% (25%, 60%)

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Patients' views of distress & interference with daily activities due to side effects in the TACT (Taxotere as Adjuvant ChemoTherapy) trial

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Introduction: TACT trial randomised 4162 women with early breast cancer to FEC-T (FEC × 4 → taxotere × 4) or Control (FEC × 8 or Epirubicin × 4 → CMF × 4). Quality of Life (QL) was an important secondary endpoint. In addition to a formal QL assessment (EORTC C30 & BR23), patients' (pts) self assessment of distress (D) & interference with daily activities (IDA) caused by toxicities during & after chemotherapy (CT) in the two arms were recorded & reported here.

Methods: Pts completed a diary card, rating each of 15 possible toxicity items as either 'did not suffer from', 'not at all', 'a little', 'quite a bit', 'very much' as D & IDA for cycles (C) 1, 5, & 8 and at 9, 12, 18 & 24 months (M). The proportion of pts at each time point rating toxicities as D &a IDA (quite a bit/very much) were compared between FEC-T & Control, a significance level of p = 0.01 allowed for multiple testing.

Results: 829 (418 FEC-T; 411 Control) pts entered the QL study. Diary Cards were completed by 458 at C1, 410 at C8, 633 at 12M & 539 at 24M. Median age was 49yrs (range 27–71).

At C1 rates of D & IDA did not differ significantly between FEC-T & Control and only vomiting, nausea & tiredness were reported as causing D & IDA by >10% pts.

During CT (C5&8) Control pts reported nausea & vomiting as causing significantly more D & IDA than FEC-T pts (approximately 3-fold difference in frequencies).

During C5&8 FEC-T pts reported pain in muscles/joints, tingling hands/feet, sore mouth & nail changes as significantly causing more D & IDA than Controls. Tiredness was reported as causing D & IDA by ⩾40% of all pts during CT, with a significant difference at C8 (Control: D 40% & IDA 43%, FEC-T: D 53% & IDA 61%).

Overall, tiredness, constipation, mouth ulcers, sore mouth, breathlessness & painful gritty eyes, caused D to >10% pts on C5&8 but only tiredness, sore mouth, breathlessness, pain in muscles/joints caused IDA for >10% pts.

After CT, toxicity rates decreased substantially; but at 24M tiredness & pain in muscles/joints were still reported as causing D & IDA by 13–22% pts, with no difference between regimens.

Conclusion: CT side effects caused more D than IDA, during CT. The majority of side effects resolved following CT but >13% pts reported a longer term impact of D & IDA from tiredness & pain in muscles/joints. More pts reported toxicities in FEC-T than control, a finding worth noting given that no overall difference in efficacy between FEC-T & control in terms of DFS was observed.

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Acupuncture for the treatment of hot flushes in breast cancer women treated with an estrogen antagonist

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Background: The object of this study was to investigate the efficacy of acupuncture in women operated for breast cancer suffering from hot flushes, a side effect of anti-estrogen medication.

Materials and Methods: In a prospective, controlled trial, 59 women suffering from hot flushes following breast cancer surgery undergoing adjuvant estrogen-antagonist treatment were randomised to either 10 weeks of traditional Chinese acupuncture or sham acupuncture. Number of hot flushes at night and daytime were recorded for 4 weeks prior to treatment, during treatment and during a 12 week follow up period. A validated health score (Kupperman index) was conducted at baseline, after 15 treatment sessions and 12 weeks post-treatment.

Results: During thetreatment period and the following 12 weeks, a 50% reduction of hot flushes both during the day and night was seen in the active treatment group, paralleled with a similar improvement in Kupperman index. Although a smaller treatment effect was observed in the sham acupuncture group during treatment, this effect could not be detected during the next 12 weeks.

Conclusion: Acupuncture seems to provide effective relief of hot flushes both day and night in women operated for breast cancer, treated post operativly with anti-estrogens. This treatment effect seems to coincide with a general health improvement measured with the validated Kupperman index.

492 Poster

Safety and efficacy of the novel antiemetic neurokinin-1 (NK-1) receptor antagonist, casopitant, in women with breast cancer (BC) receiving moderately emetogenic chemotherapy (MEC) – subgroup analysis from a randomized, double-blind, placebo-controlled phase II trial

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Background: Casopitant is a potent, selective, NK-1 receptor antagonist that increased the rate of control of chemotherapy-induced nausea and vomiting (CINV) when added to an ondansetron/dexamethasone (OND/DEX) prophylactic regimen administered to patients (pts) with solid tumors receiving MEC in a phase II trial (J Clin Oncol. 2006;24:471s. #8512). The current analysis examines the safety and efficacy in the subgroup of women with BC.

Methods: Pts received OND 8 mg PO BID D1–3 + DEX 8 mg IV D1 with either active control, casopitant 50 mg, 100 mg, or 150 mg PO D1–3. Additionally, 2 exploratory arms were included to evaluate alternate dosing of casopitant and OND (150 mg D1 only (with OND/DEX) and casopitant 150 mg D1–3 with OND 16 mg/d). Pts with BC received MEC consisting of ⩾1 of the following (mg/m^2): cyclophosphamide (C) 500–1500 with other MEC; C 750–1500 if given alone or with non- or minimally emetogenic agents; doxorubicin (A) ⩾60; or epirubicin (E) ⩾90. Adjuvant regimens were not permitted. The primary endpoints were complete response (CR; no vomiting, retching, rescue medications, or premature withdrawal) and rate of significant nausea (⩾25 mm on VAS) during the first 120 hrs after chemotherapy.

	120 h CR rate (%)					
	Active control	Casopitant				
		50 mg	100 mg	150 mg	150 mg D1*	150 mg + OND 16 mg/d*
Primary analysis (N = 723)	69	81	79	84	79	84
Pts with BC (N = 176)	26 (69)	38 (82)	32 (75)	23 (87)	30 (73)	27 (81)

*Exploratory arms, not included in primary analysis.
† P = 0.012.

Results: Of the 176 pts with BC receiving MEC, the majority received a combination of AC or EC (n = 102) or a taxane (n = 37). In the primary