Material and Methods: From January, 2008, to December, 2009, 455 patients from 99 participating sites were randomized to lapatinib, trastuzumab or both drugs for 6 weeks (no chemotherapy). After this biological window, patients continued on the same targeted therapy plus weekly paclitaxel for a further 12 weeks until surgery. After surgery, patients received 3 cycles of adjuvant FEC followed by the same anti-HER2 therapy for a further 34 weeks.
FDG PET/CT was performed in a subset of 85 patients at baseline, week 2 and week 6 for early assessment of response to targeted therapies alone without chemotherapy in patients enrolled in 30 qualified sites. Central validation of acquisition parameters and imaging analysis were performed by two blinded reviewers. Description of the lesions includes localization, metabolic volume, SUVmax and SUVmean. Metabolic parameters at week 2 and week 6 will be compared to baseline. Patients will be classified as responders in case of tumour metabolic complete response (mCR) or partial response (mPR) and non-responders in case of metabolic stable disease (mSD). The aim of this analysis is to test whether metabolic response with anti-HER2 therapies alone predicts pCR at the time of surgery.
Results: The last breast surgery was performed in May 2010. FDG PET/CT data cleaning and analysis will be completed by April 2011 and final results on the predictive value of early FDG PET/CT in this large phase III study will be presented at the meeting.
Conclusions: FDG PET/CT data analysis will be discussed at the meeting according to the results obtained.

5014 ORAL

High Risk of Non-sentinel Node Metastases in a Group of Breast Cancer Patients With Micrometastases in the Sentinel Node

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Background: Axillary lymph node dissection (ALND) in breast cancer patients with positive sentinel nodes (SN) is under debate. The aim of this study was to identify a group of breast cancer patients with micrometastases or isolated tumour cells (ITC) in the SN where ALND might still be recommended because of a high risk of non-sentinel node (NSN) metastases. Furthermore, the aim was to identify a group of patients with a minimal risk of NSN metastases, justifying omission of ALND in any case.
Materials and Methods: A total number of 1577 breast cancer patients with micrometastases and 304 patients with ITC in the SN, operated on between 2002–2008 with sentinel lymph node dissection and subsequent ALND, was identified retrospectively using the nationwide Danish Breast Cancer Cooperative Group database. Data was validated using original pathology files and specimens. The risk of NSN metastases was calculated according to clinicopathologic variables in univariate and multivariate logistic regression analyses.
Results: 18% of patients with micrometastases and 9% of patients with ITC had NSN metastases. The risk of NSN metastases in patients with micrometastases was significantly related to tumour size, lymphovascular invasion, hormone receptor status, location of tumour in the breast and proportion of positive SN in the multivariate analysis. A model based on these risk factors identified 5% of patients with a risk of NSN metastases as high as 37%. On the other hand, the model was only able to identify less than 10% of patients with a very low risk of NSN metastases.
The risk of NSN metastases in patients with ITC in the SN was significantly related to age, tumour size and proportion of positive SN in the multivariate analysis. No subgroup of patients with ITC had a risk of NSN metastases over 25%. Patients with tumour size <2 cm and one or more negative SN, corresponding to 34% of patients with ITC, had a very low risk of NSN metastases. Omission of ALND in this group would result in a false negative rate of only 7%.
Conclusions: We have identified a group of patients with micrometastases in the SN with high risk of NSN metastases on nearly 40%, comparable to the risk for patients with macrometastases. ALND may still be recommended in these patients despite new evidence indicating omission of ALND to be safe in selected patients with positive SN. In patients with ITC no subgroup had a risk of NSN metastases over 25%, whereas 1/3 of the patients had a very low risk of NSN metastases, justifying omission of ALND.

5015 ORAL

Age Specific Competing Mortality in Breast Cancer Patients – a TEAM Study Analysis

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Background: In addition to tumour related prognostic factors, characteristics of breast cancer patients may affect outcome. The aim of this study was to assess competing mortality in postmenopausal women with early breast cancer of the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial.
Material and Methods: 9,766 women were enrolled in the TEAM trial, randomized to either Exemestane 25 mg daily for 5 years or Tamoxifen 20 mg daily for 2.5−3 years, followed by Exemestane 25 mg daily for 2−2.5 years. Five-year results showed no difference in outcome between both arms (*Lancet* 22;377:321, 2011) enabling to analyze causes of mortality in the entire population. Patients were stratified by age at diagnosis (<65, 65−74, ⩾75 years) and survival was calculated by a Cox Proportional Hazard Model (A) as well as a Fine and Gray Model for competing mortality (B).
Results: All patients had hormone receptor positive tumours, 50% had node negative disease, 68% received radiotherapy, and 36% received chemotherapy. After a median follow up of 5.1 years, multivariable analysis using model A showed a higher proportion of breast cancer specific and non breast cancer related mortality with increasing age ($p < 0.001$). Using model B, which takes into account the risk of competing mortality, a higher breast cancer mortality over age was confirmed ($p < 0.001$) (Table 1).
Conclusions: Though the chance of dying from other causes than breast cancer was much higher in elderly patients, breast cancer mortality increased with higher age as well. Additionally, survival analyses evaluating the risk of competing mortality confirmed a higher absolute breast cancer mortality in the elderly, suggesting the possibility of suboptimal treatment. These data underline the need for optimal, individualized treatment of the elderly breast cancer patient, taking into account biological age and life expectancy, in order to improve breast cancer outcome in all age groups.

Table 1. Mortality analyses

	Breast cancer mortality			Non breast cancer mortality		
	5 yrs %	HR* (95% CI)	p value	5 yrs %	HR (95% CI)	p value
Cox Regression			**<0.001**			**<0.001**
<65 years	5	1 (reference)		1	1 (reference)	
65−75 years	6	1.23 (1.09–1.61)		5	2.56 (1.94–3.37)	
⩾75 years	8	1.86 (1.44–2.40)		14	7.08 (5.32–9.41)	
Fine and Gray			**<0.001**			**<0.001**
<65 years	5	1 (reference)		1	1 (reference)	
65−75 years	6	1.22 (1.00–3.26)		5	2.46 (1.86–3.25)	
⩾75 years	8	1.50 (1.16–1.94)		14	6.57 (4.90–8.80)	

*HR (hazard ratios) adjusted for country, histological grade, tumour size, nodal staus, ER, PgR, type of surgery, radiotherapy and chemotherapy.

Poster Discussion Presentations (Mon, 26 Sep, 11:00−12:00)

Breast Cancer

5016 POSTER DISCUSSION

BIG 1-98 Update: Evaluating Letrozole and Tamoxifen Alone and in Sequence at 8 Years Median Follow-up for Postmenopausal Women With Steroid Hormone Receptor-Positive Breast Cancer

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Background: BIG 1-98 is a Phase III randomized, double-blind trial comparing letrozole (Let), tamoxifen (Tam) and sequences of Let and Tam as adjuvant endocrine therapy for postmenopausal women with endocrine-responsive early breast cancer. In 2005 the superiority of Let over Tam for

disease-free survival (DFS) and distant recurrence-free interval (DRFI) was demonstrated and here we report the results after 8 years median follow-up. Following the 2005 results, the treatment assignment was unblinded for patients randomized to Tam alone, and over one-quarter of these patients opted to receive Let. The other three arms remain blinded.
Methods: 8010 patients were randomized to the trial. 57% of patients had node-negative (N−) disease and 25% received chemotherapy (13% of N− and 43% of N+). The monotherapy comparison includes patients randomized to Tam × 5 yrs (Tam5) or Let × 5 yrs (Let5). The sequential treatment comparison includes patients randomized to Let5, Tam × 2 yrs followed by Let × 3 yrs (Tam2–Let3), or the reverse (Let2–Tam3). Cox models and Kaplan–Meier estimates with inverse probability of censoring weighting (IPCW) are used to adjust for selective crossover in the Tam5 arm.
Results: This update includes 2074 DFS events compared with 1569 at the prior protocol-specified update two years ago. Compared with Tam5, Let5 significantly improved DFS, overall survival (OS), and DRFI. 8-year estimates for Let5 vs Tam5 were 76% vs 72% for DFS and 85% vs 81% for OS. All monotherapy comparisons are also statistically significant (P < 0.05) using the intent-to-treat analysis. Results for the sequential comparisons to Let5 are in the table.

Comparison	N	DFS			OS			DRFI		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Let5 vs Tam5	2463 2459	0.82	0.74–0.92	0.0002	0.79	0.69–0.90	0.0006	0.79	0.68–0.92	0.003
Tam2-Let3 vs Let5	1548 1546	1.07	0.92–1.25	0.36	1.10	0.90–1.33	0.36	1.23	0.99–1.52	0.06
Let2-Tam3 vs Let5	1540 1546	1.06	0.91–1.23	0.48	0.97	0.80–1.19	0.80	1.14	0.92–1.42	0.24

Conclusions: At a median follow-up of 8 years, for postmenopausal women with endocrine-responsive early breast cancer, adjuvant endocrine treatment with Let5 has superior disease control and overall survival compared with Tam5. Let5 tends to be superior to Tam2–Let3, especially for control of distant recurrence among patients at higher risk of early relapse. Let2–Tam3 had similar outcome to Let5.

5017 POSTER DISCUSSION

Efficacy of Endocrine Therapy Regimens in Major Histological Subtypes of Breast Cancer − a TEAM Study Analysis

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Introduction: Individual targeted breast cancer therapy is developing rapidly. Studies on adjuvant chemotherapy suggest different efficacy based on breast cancer subtypes, with ductal breast carcinomas more likely to respond to chemotherapy than their lobular counterparts. Similar efficacy of adjuvant endocrine therapy (ET) in ductal and lobular carcinoma has been reported. However, data on the efficacy of different adjuvant endocrine therapy regimens by histological subtypes is still lacking. The aim of this study was to assess efficacy of two ET regimens in infiltrating ductal (IDC) and lobular carcinomas (ILC).
Methods: 9,766 women were randomized to exemestane 25 mg once-daily for 5 years or tamoxifen 20 mg once-daily for 2.5−3 years, followed by exemestane 25 mg once-daily for 2.5−2 years in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. Histological subtype was locally assessed. Disease free survival (DFS) was defined as time from randomization to the earliest documentation of disease relapse or death from any cause. Relapse free period (RFP) was defined as time to earliest documentation of disease relapse or death due to breast cancer.
Results: 7231 patients with ILC (n = 1126) and IDC (n = 6105) were included in the present analysis. Patients with ILC were older (p = 0.004), and more often had larger tumours, unknown tumour grade, and axillary lymph node involvement (all p values < 0.001). In ILC patients, univariate DFS and RFP were similar in both treatment arms (p = 0.361; p = 0.384 respectively). In IDC patients, DFS and RFP were also similar for both arms (p = 0.824; p = 0.452 respectively). Additional analysis confirmed no interaction between randomization and histological subtype (p = 0.389; p = 0.632 respectively).
Discussion: The present study did not demonstrate different efficacies in endocrine therapy regimens for tumour subtypes. With the growing interest in patient-tailored treatment, it is essential to establish individual benefits from targeted therapies.

Table 1. Disease free survival (DFS) and relapse free period (RFP)

	% 5 y survival	HR (95% CI)	p value
DFS			
Ductal			0.824
T-E	86	1 (reference)	
E	86	1.01 (0.89–1.51)	
Lobular			
T-E	82	1 (reference)	0.361
E	83	0.88 (0.67–1.15)	
RFP			
Ductal			0.452
T-E	98	1 (reference)	
E	98	0.94 (0.81–1.10)	
Lobular			
T-E	96	1 (reference)	0.384
E	98	0.87 (0.63–1.20)	

T: tamoxifen; E: exemestane.

5018 POSTER DISCUSSION

No Effect of Adjuvant Chemotherapy on the Prognosis of Hormonally Treated Postmenopausal Women With Pure or Mixed Type Lobular Breast Cancer

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Background: The effect of adjuvant chemotherapy in addition to hormonal therapy on the prognosis of postmenopausal women with breast cancer was analyzed by primary histology, including invasive ductal carcinoma (IDC), pure invasive lobular carcinoma (ILC) and mixed type ILC.
Material and Methods: All women with primary non-metastatic invasive breast cancer from ductal, pure lobular or lobular-mixed origin, aged 50 to 69 years who were diagnosed in the period 1995 to 2008 were selected from the database of the Netherlands Cancer Registry. Patients were divided in two groups: those who received hormonal therapy only versus hormonal therapy in combination with adjuvant chemotherapy. Cox proportional hazards analyses were carried out to determine the impact of chemotherapy in addition to hormonal treatment, for each histological entity separately and interaction between use of chemotherapy and histological type was tested.
Results: In total 19,937 patients with IDC, 3,733 patients with pure ILC and 1,398 patients with mixed type ILC were included. Patient groups were comparable with respect to the use of adjuvant systemic treatment. Among the patients with IDC a significant difference in ten-year overall survival was observed between patients treated with hormonal therapy only, versus hormonal therapy combined with chemotherapy (68% vs. 74%, p < 0.001). In contrast, this effect was not observed in patients with pure ILC (67% vs. 66%, respectively, p = 0.86) or mixed type ILC (73% vs. 67%, respectively, p = 0.33). The hazard ratio (HR) for death among the patients with IDC receiving chemotherapy in addition to hormonal treatment was 0.70 (95% CI, 0.64–0.76, p < 0.0001), as compared to those receiving hormonal treatment alone. In patients with pure or mixed type ILC, however, these HR's were 1.00 (95% CI, 0.82–1.21, p = 0.97) and 0.98 (95% CI, 0.70–1.33, p = 0.83), respectively. A statistically significant interaction was observed between the use of adjuvant chemotherapy and histological tumour type. In a model including patients with ILC and IDC, the p-value for interaction was 0.01 and in a model including patients with mixed-type ILC and IDC the p-value for interaction was 0.004.
Conclusions: Postmenopausal patients with ILC have an inferior response to adjuvant chemotherapy as compared with IDC and actually do not benefit from this additional therapeutic modality. Patients with mixed type ILC seem to behave in a similar way as those with pure ILC. Guidelines dictating the administration of adjuvant chemotherapy in pure ILC and mixed type ILC should be revised in order to prevent chemotherapy-related morbidity and lower costs.