count was 16.23 (SD+ 7.156). Age, pathologic classification and use of taxanes did not influence nodal count. A non-significantly higher number of insufficient ALND were observed in complete tumoral responses (37.5% vs 21%, p = 0.203). Miller and Payne grades C and D in the lymph nodes were associated with an insufficient nodal count (34.4% in Miller and Payne C−D vs 15.1% in A−B, p = 0.005).

Conclusion: as reported by other authors, in our institution, nodal counts are more frequently insufficient in ALND following neoadjuvant chemotherapy than in ALND performed in patients, not receiving chemotherapy. A non-significant trend to a lower nodal count was seen in patients with pathologic complete response in the tumour. A significant lower nodal count was seen in patients with chemotherapy changes in the pathology of lymph nodes (C and D Miller and Payne grades). This suggests that chemotherapy on lymph nodes make more difficult for surgeons to perform ALND and/or for pathologists to identify lymph nodes.

Friday, 18 April 2008 12:30–14:30

POSTER SESSION

Targeted therapies/Advanced disease

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FDG-PET-CT in detecting locoregional disease and distant metastasis in high risk breast cancer patients

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Background and Aim: Conventional staging in breast cancer, consisting of chest-X-ray, ultrasound of the liver and bone scintigraphy, is often considered not to be sufficiently sensitive nor specific, especially with respect to detection of metastases in the internal mammary lymph nodes (IMN). The aim of this study is to evaluate the value of FDG-PET-CT in detecting locoregional disease and distant metastasis in breast cancer patients, in whom conventional screening is indicated according to the Dutch guidelines.

Material and Methods: Between June 2005 and Nov 2007 FDG-PET-CT scanning was added to conventional staging in 28 patients, prior to therapy. In nine patients (group 1) with high risk early stage primary breast cancer (grade III, tumour diameter >3 cm, clinically node positive, age <40 yrs), 4 patients with locally advanced breast cancer (group 2) and 14 patients with locoregional recurrence (group 3) FDG-PET-CT scans were made as a staging procedure. FDG-PET-CT data were analyzed by an experienced radiologist (RB) and nuclear medicine physician (MvK).

Results: A change in T or N stage was made in 10 patients (36%, 95% CI 16−56). The IMN contained a PET positive lesion in 4 patients (14%, 95% CI 0−29) (1 in group 1 and 3 in group 3). Two lesions were histologally proven, 1 was FNA negative and in 1 patient histology was not obtained because of otherwise metastatic disease. Three patients were treated with radiotherapy to the IMN. Distant metastatic disease was found in 5 patients (18%, 95% CI 2−34). One patient had multiple bony lesions; four patients had mediastinal lymph nodes (2 histologically positive, 2 not biopsied). The detection of distant metastases led to minimalisation of locoregional treatment. M1 status was converted to M0 in 4 patients (14%, 95% CI 0−29).

Conclusions: FDG-PET-CT identified metastases to the IMN in 14% of the patients, which had not been identified by conventional staging. Overall stage migration occurred in 36% of the patients, which enabled a better tailoring of the treatment.

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Disease progression as a predictor of overall survival in metastatic breast cancer: a meta-analysis

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Background: The relationship between disease progression endpoints and overall survival (OS) has been demonstrated in colorectal, colon, and non-small cell lung cancers. Patient access to novel and efficacious therapies for metastatic breast cancer (MBC) could be expedited if disease progression were documented as a valid surrogate outcome for OS in pivotal clinical trials. We assessed the association between time to tumor progression (TTP) and progression-free survival (PFS) and OS in randomized controlled trials (RCTs) for MBC.

Methods: A literature search retrieved all RCTs since 1994 in patients with MBC (first-line and refractory) in which both progression endpoints and OS were reported. Summary data on trial and patient characteristics were abstracted. Analyses across studies were performed using the hazard rate ratio where reported or the ratio of median months to event as an approximation of study effect sizes. Logarithm of the effect was regressed without an intercept and weighted by sample size for each study.

Results: A wide range of treatment types was represented in 67 studies covering 17,081 MBC patients. The exponentiated regression of study effect on survival by study effect on progression yielded the equation: $Effect_{Survival} = (Effect_{Progression})^{0.38}$ R^2(adjusted) = 0.34.

Since the confidence interval for the slope parameter does not include zero (95% CI: 0.23, 0.49), we infer that treatment effects on progression will yield treatment effects on survival, though the difference between groups is not expected to be as large. Four of the studies identified all patients as HER2+; in this subset, the association between progression and survival benefit was stronger (slope = 0.36; CI: 0.19, 0.53; R^2 = 0.92).

Conclusions: These results demonstrate that treatment differences in time to progression endpoints (TTP/PFS) observed in MBC trials are expected to coincide with differences in OS as previously established in other tumor types.

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Lapatinib plus capecitabine versus capecitabine alone for ErbB2-positive metastatic breast cancer (MBC) – Quality of Life (QOL) assessment

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Background: A Phase III randomized open-label multicenter study compared the treatment of lapatinib plus capecitabine (L+C) versus capecitabine alone (C) in adult women with ErbB2+ MBC who had received prior therapy which included an anthracycline, a taxane and trastuzumab. The study was closed early to new enrollment after 399 subjects when the primary endpoint was achieved at an interim analysis. This analysis focuses on the impact of treatments on health-related QOL.

Methods: QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and the EuroQol (EQ-5D) questionnaire. Outcome measures included the FACT-B total score, FACT-general (FACT-G) score, trial outcome index (TOI) score, EQ-5D utility score, and EQ-5D visual analog scale (VAS) score. Higher scores indicate better QOL. Patients completed the questionnaires at the screening visit, every 6 weeks for the first 24 weeks, every 12 weeks thereafter and at study withdrawal. Changes from baseline scores were analyzed for the ITT population using analysis of covariance with baseline value as a covariate. Missing post-baseline data were imputed using the last observation carried forward method.

Results: The study randomized 198 subjects to the L+C arm and 201 subjects to the C arm. At the enrollment close, nearly half of the subjects had completed the Week 12 assessment and one-fifth had completed the Week 24 assessment. Point estimates for all scores were generally higher

for the L+C arm versus the C arm. Group differences in adjusted mean change from baseline, although not statistically significant ($p > 0.05$), were consistently in favor of the L+C arm and ranged from 0.7 to 2.2 (FACT-B), 0.9 to 1.5 (FACT-G), 0.2 to 1.5 (TOI), 0.00 to 0.03 (EQ-5 utility) and 0.3 to 1.8 (ED-5D VAS) over a 24-week follow up.

Conclusions: The two treatment groups appear to be similar in HRQOL scores, suggesting that there was no detriment to quality of life in patients receiving combination therapy (lapatinib plus capecitabine) compared with those receiving monotherapy (capecitabine) in this heavily pre-treated patient population.

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Phase II evaluation of the efficacy and safety of trastuzumab plus pertuzumab therapy in patients with HER2-positive metastatic breast cancer that had progressed during trastuzumab treatment

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Background: Pertuzumab (P) is the first of a new class of HER dimerization inhibitors (HDI), targeting multiple HER pathways by binding to HER2 to block both homo- and heterodimerization of HER2 and other HER receptors. Trastuzumab (Herceptin®, H) binds to a different epitope and xenograft studies indicate that the complementary mechanisms of action of P and H have a synergistic effect when combined. This study investigates the efficacy and safety profile of H plus P in previously treated patients (pts) with HER2-positive MBC.

Material and Methods: Pts with measurable, centrally tested HER2-positive MBC who had received ⩽3 prior lines of therapy (including adjuvant therapy), had progressed during prior H treatment, and had a baseline LVEF ⩾55% that had not declined to <50% with H therapy, were eligible for this single-arm, Simon-type, two-stage trial. Consenting pts received H at 2 mg/kg qw (4 mg/kg loading dose [LD]) or 6 mg/kg q3w (8 mg/kg LD) plus P at 420 mg q3w (840 mg LD) starting within 9 weeks of the last dose of H. LVEF was regularly assessed.

Results: Currently 61 pts have received ⩾1 dose of therapy. Interim efficacy analysis in 33 eligible pts (⩾1 tumor evaluation on treatment) was: CR 1 (3%); PR 5 (15%); SD ⩾6 months 7 (21%); SD <6 months 10 (30%); and PD 10 (30%). Overall response rate was 18% and clinical benefit rate was 39%. Of 61 pts evaluable for safety, 54 had ⩾1 AE. Frequent (⩾30%) grade 1/2 AEs included diarrhea (59%), pain (43%), nausea/vomiting (36%), mucositis (33%), skin (31%), and rash (30%). Grade ⩾3 AEs included DVT, UTI, and rash (all n = 1) and in 1 pt, increased ALP, hyperbilirubinemia and hepatic failure. There was only one treatment-related grade 3 AE (diarrhea), which resolved and treatment was continued. Two pts experienced a fall in LVEF of ⩾10% to <50% (1 centrally confirmed). Both pts remained asymptomatic and were withdrawn from the study due to PD. No pts withdrew due to cardiac events or treatment-related AEs.

Conclusions: The combination of H plus P is active and well tolerated in pts with HER2-positive MBC that has progressed during prior H therapy. Most AEs were grade 1 or 2 and no clinically significant cardiac events were observed in 61 pts. Further studies are currently underway to fully evaluate the use of this agent in breast cancer.

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Final results of a phase II study of bevacizumab plus docetaxel for the first-line treatment of metastatic breast cancer (TORI-B01)

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Background: First line treatment (Tx) of metastatic breast cancer (MBC) with paclitaxel (P) plus bevacizumab (B) significantly improves response rates (RR) and progression free survival (PFS) compared to P-alone. Docetaxel (D) is one of the most active agents for MBC, with RR between 30−60%. To assess the activity of D + B, a multicenter, phase II trial was begun. The primary endpoint was time to progression (TTP). Secondary endpoints were RR, duration of response, overall survival (OS) and safety.

Methods: Pts with Her2/neu negative MBC, previously untreated in the metastatic setting were eligible. Adjuvant Tx with a taxane was allowed if ⩾12 mos had lapsed since its completion. This trial began as a 2-arm study with a D-alone arm. When B became widely available, it was converted to a 1-arm, open-label trial of D+B and pts enrolled in the D-alone arm were given the option to cross-over to D+B. All pts received B 15 mg/kg IV and D 75 mg/m^2 IV q3 wks. Tx continued until disease progression (PD), unacceptable toxicity or consent withdrawal.

Results: From 3/2005 to 9/2006, 76 pts were enrolled. Two pts were ineligible. Seven pts were initially randomized to D-alone. Six of these pts chose to cross-over to D+B and are only included in the safety analysis. Efficacy data are based on the intent to treat (ITT) population of 67 pts. The median (med) pt age was 57. The confirmed objective RR is 50.7% (34/67) with 7.5% (5/67) complete responses (CR) and 43.3% (29/67) partial responses (PR). 19.4% (13/67) pts had stable disease (SD) as their confirmed best response. With 18.1 mos med follow up, the med TTP is 9.3 months, [95% CI (8.2, 12.4)]. The TTP for hormone receptor (HR)-negative tumors was 6.4 mos [95% CI (4.1, 8.2)] versus 12.6 mos [95% CI (9.3−15.8)] for HR(+) tumors (Log rank test $p = 0.0010$). The median OS is 25.7 mos [95% CI (20.1, NR)]. Six pts remain on study, including 1 pt who has completed 40 cycles thus far (range 20−40 cycles). The most common Gr 3/4 AEs were neutropenia (25/75), leukopenia (16/75), fatigue (14/75), hypertension (6/75), and infection (7/75). There were 2 cases of Gr 3/4 epistaxis, 1 Gr 3 proteinuria and 1 Gr 3 DVT.

Discussion: D + B was generally well-tolerated with no new safety concerns, manageable toxicity and promising efficacy results.

This study was supported by unrestricted research grants from Sanofi-Aventis & Genentech.

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Phase III study of gemcitabine (G) plus paclitaxel (T) versus T in patients with metastatic breast cancer (MBC) – Post-study chemotherapy (PSC) trend analysis

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Background: This Phase III trial was designed to compare safety and efficacy of G plus T versus single-agent T in patients (pts) with MBC. Earlier reports of this trial described a statistically significant advantage in response, time-to-progression and overall survival (OS) for the GT combination with a manageable toxicity profile. While the benefits of first-line chemotherapy for MBC are well established, the clinical impact of second and multi-line chemotherapy remains controversial. We performed an exploratory analysis of PSC and the effect of PSC on OS for pts in the current Phase III trial.

Materials and Methods: Pts enrolled with unresectable MBC, one prior regimen of anthracycline-based chemotherapy, and KPS ⩾70 were randomized to receive either GT (G 1250 mg/m^2 D1, 8; T 175 mg/m^2 D1) or T (175 mg/m^2 D1) every 21 days until disease progression (PD) or undue toxicity. After completing treatment, pts with PD were given follow-up assessments every 4 months until a total of 440 death events were recorded (the analysis reported here). Details of any PSC were recorded at each visit. Survival results were analyzed by the Kaplan–Meier and Cox proportional hazards methods.

Results: Following study discontinuation, 56% of pts in the GT arm and 60% of pts in the T arm received at least one line of PSC and 20% of pts in both arms received ⩾3 lines. Use of single-agent PSC was more common in both treatment arms (GT, 69%; T, 62%) compared with combination PSC. Pts received over 25 different PSC agents. The most common PSC agents were vinorelbine (GT, 32%; T, 35%), capecitabine (GT, 28%; T, 22%), docetaxel (GT, 15%; T, 14%), 5-fluorouracil (GT, 11%; T, 17%), and gemcitabine (GT, 5%; T, 17%). For pts receiving PSC, median OS was 20.2 months in the GT arm and 18.9 months in the T arm. For pts not receiving PSC, median OS was 14.2 months in the GT arm and 10.5 months in the T arm. Comparison of PSC versus no PSC in the GT arm produced a hazard ratio (HR) of 0.84 (95% CI: 0.64−1.10; $p = 0.197$). However, comparison of PSC versus no PSC in the T arm had a HR of 0.66 (95% CI: 0.5−0.86; $p = 0.003$).

Conclusions: Over 40% of pts receiving first-line GT or T did not receive PSC. Exploratory analysis of OS did not find significant evidence that OS for GT-treated pts was impacted by PSC. However, T-treated pts not receiving PSC had a significantly reduced survival outcome. The implications of these results will be discussed.