patients with relative dose intensity (RDI) ⩾ 85%, with secondary objectives of incidences of dose delays and dose reductions due to neutropenic events, toxicity and disease free survival.
Results: Between May 2005 and May 2006 51 pts were recruited (25 Arm A, 26 Arm B). Baseline demographics and disease characteristics are shown in the table, as is RDI and the incidence of hematological toxicities.
Conclusions: In this study, proportion of patients with RDI ⩾ 85% was 96% and 89% in pegfilgrastim augmented dose-dense FEC75 and FEC90 arms. No patient experienced febrile neutropenia and there were only single occurrences of grade 3−4 leukopenia and neutropenia. Thus, within the short time period assessed, these initial data suggest that both regimens are safe in the adjuvant treatment of early breast cancer.

Oral presentations (Tue, 25 Sep, 09.00−11.00)
Breast cancer – advanced disease

2096 ORAL

Lapatinib (L) plus Capecitabine (C) in HER2+ advanced breast cancer (ABC): report of updated efficacy and gene-array data

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Background: EGF100151 demonstrated L+C improved TTP relative to C alone in women with HER2+, trastuzumab-exposed ABC [Geyer, NEJM 2006; 355(26)]. We report updated efficacy results and correlative studies to determine if differential gene expression levels are associated with clinical benefit of L+C.
Methods: Tumor blocks were available for 217/399 patients; sufficient mRNA was extracted from103/217 patient tumor blocks for evaluation of gene expression by qRT-PCR and by Affymetrix HU133 plus 2.0 gene expression arrays. SpotFire™ DecisionTree analysis was performed on the qRT-PCR data to determine the genes significantly associated with RR; genes were further analyzed for association with TTP using Kaplan Meier survival analyses. Preliminary gene array data were analyzed, to date only in the combination arm, using a Wilcoxon's test (cut-off $p < 0.01$) to determine genes with significant differential expression between the responders and non-responders.
Results: Efficacy results as of April 3, 2006: TTP L+C 27 wk vs C 19 wk, HR 0.57 [0.43, 0.77], $p = 0.00013$; ORR L+C 24% vs C 14%, Odds Ratio 1.9 [1, 1.34], $p = 0.017$; OS L+C vs C HR 0.78 [0.55, 1.12], $p = 0.177$; progression in CNS L+C 2% vs C 11%, $p = 0.0445$. Amongst 103 patients with mRNA data, there were 19 responders (PR = 19), 26 non-responders (SD = 20, PD = 6) and NE = 10 in L+C; 5 responders (PR = 5), 22 non-responders (SD = 20, PD = 12) and NE = 8 in C. Preliminary analysis of gene array data show elevated baseline HER2 mRNA expression correlates with response to L+C ($p < 0.01$) in L+C. This finding was confirmed by qRT-PCR data where elevated baseline HER2 mRNA expression is associated with higher RR as well as longer TTP ($p < 0.0001$) with L+C. In addition, gene array data revealed that patients with elevated baseline FOX3A mRNA levels and reduced baseline BCL-2 mRNA responded to L+C in the combination arm alone; consistent with preclinical response data in breast cancer cell lines.
Conclusion: Updated efficacy results confirm the prior demonstrated benefit of L+C vs C and provide evidence for systemic anti-HER2 therapy effects on the development of CNS metastases. Preliminary data suggest a correlation between elevated HER2 mRNA levels and RR/TTP. In addition, preliminary gene array data suggest that patients whose tumours have increased regulation of HER signaling and induction of apoptotic pathways gain greater clinical benefit from treatment with L+C. Additional array analyses will be discussed from both treatment arms.

2097 ORAL

Biomarker analysis of lapatinib with paclitaxel versus paclitaxel as first-line treatment in 580 patients with metastatic breast cancer

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Background: Lapatinib is an oral tyrosine kinase inhibitor of EGFR/HER2 that was recently approved in US for use in combination with capecitabine for HER2-overexpressing (HER2+) advanced/metastatic breast cancer (BC) pretreated with taxanes, anthracyclines, and trastuzumab-based therapy. Paclitaxel has shown activity alone and in combination for HER2+ BC. We report here an analysis on HER2, ER, and PR for 580 patients (pts) with incurable Stage IIIb/IIIc/IV BC at first diagnosis or relapse whose HER2 status was unknown or negative (IHC0/1+ or FISH−) at study entry.
Methods: Between Jan 2004 and Jul 2005, 580 first-line pts from 24 countries were stratified by metastatic site and randomized 1:1 to 1500 mg lapatinib QD + 175 mg/m^2 paclitaxel q3w or placebo QD + 175 mg/m^2 paclitaxel q3w. Primary endpoint was TTP; secondary endpoints were AEs, ORR, PFS, CBR, RFS, and OS. Archived tumor tissue and/or slides obtained from the most recent biopsy were centrally analyzed in blinded fashion for HER2 (IHC and FISH) and ER/PR (IHC). Based on these results, pts were categorized into 3 groups: HER2+, luminal, and basal.
Results and Conclusions: Biomarkers were correlated with clinical efficacy in 579 pts; 542 (93%) pts had tissue available for central analysis. 91 (18%) pts were determined to be HER2+ by FISH or IHC3+. In the HER2+ subset, a statistically significant improvement was observed in lapatinib + paclitaxel vs paclitaxel-treated patients in both median TTP (35.1 v 25.1 wks, HR = 0.57, 95% CI 0.34, 0.93, $p = 0.0107$) and ORR (59.6% v 35.9%, odds ratio=2.9, 95% CI 1.1, 7.9, $p = 0.027$). Efficacy data in subgroups of patients based on hormone receptor expression levels and breast cancer subtype will be reported. Overall survival data will be available at the time of presentation.
In conclusion, lapatinib in combination with paclitaxel demonstrated statistically significant clinical activity as measured by TTP/PFS and ORR in a targeted population of HER2+ pts with metastatic BC.

2098 ORAL

BCIRG 007: First overall survival analysis of randomized phase III trial of trastuzumab plus docetaxel with or without carboplatin as first line therapy in HER2 amplified metastatic breast cancer (MBC)

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Background: Based on preclinical synergism between docetaxel (T), carboplatin (C) and trastuzumab (H), BCIRG conducted a phase III trial in HER2-positive MBC to evaluate efficacy and safety of H in combination with T or TC.
Methods: 263 patients (pts) with HER2 FISH+ MBC were randomized to TH (H with T 100 mg/m^2) or TCH (H with T 75 mg/m^2 and C AUC=6). Chemotherapy was given every 3 weeks (q3w) for 8 cycles with weekly H at 2 mg/kg (loading dose of 4 mg/kg) followed by H q3w at 6 mg/kg until progression. Pts were stratified by centre and prior (neo) adjuvant taxane chemotherapy. Primary endpoint was Time To disease Progression (TTP). Secondary endpoints include overall survival, response rate, duration of response (DR), clinical benefit (CB) and safety. In addition, a sub study on Serum HER2 Extra Cellular Domain (ECD) was conducted on the 89% of subjects with levels >15 ng/mL at the time of metastatic disease (86% in TH-treated subjects vs. 92% in TCH-treated subjects).
Results: 131 pts were treated in each arm Pt characteristics were well balanced in both groups. A first efficacy analysis was conducted at 204 events. There was no significant difference between TH and TCH in median TTP (11.1 vs 10.4 mos, $p = 0.57$), ORR (73% in both arms), DR (10.7 vs 9.4 mos) and CB (67% in both arms). At 39 months of median follow-up, median overall survival was 36.40 and 36.57 months in TH and TCH arms respectively. More patients on TCH received the max number of chemotherapy cycles, and numerically fewer patients on TCH discontinued treatment as a result of non hematological toxicity. The most common gr 3/4

toxicities were: neutropenic infection that was 16.8% vs 9.2% respectively for TH and TCH, thrombocytopenia (2% vs 15%), asthenia (5% vs 12%), anemia (5% vs 11%), and diarrhea (2% vs 10%). Two pts died (1.5%) due to sepsis in TCH. Absolute LVEF decline >15% were seen in 5.5% vs 6.7% of pts. One pt (0.8%) had a symptomatic CHF in TH arm. The serum HER2 ECD analysis is underway and will be presented.
Conclusion: Both TH (T 100) and TCH (T 75) were highly effective treatment regimens in women having HER2-positive MBC, demonstrating high response rates, median TTP >10 months, and median overall survival >36 months in both TH and TCH. Cardiac toxicity was no significant problem with either treatment.

2099 ORAL

Multiple lines of trastuzumab provide a survival benefit for women with metastatic breast cancer: results from the Hermine cohort study

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Background: The efficacy and safety of trastuzumab (Herceptin®; H) in combination with taxanes have been demonstrated in clinical trials of patients (pts) with HER2-positive metastatic breast cancer (MBC). There is considerable interest in the efficacy of continuing H after disease progression. Data from the Hermine cohort study of H for MBC in routine clinical practice were analysed to determine whether continuation of H is beneficial.
Material and Methods: Hermine was an observational French cohort study of pts with HER2-positive MBC who began their initial H treatment between January and December 2002. Study end points included duration of treatment, progression-free survival (PFS) and overall survival (OS). Minimum follow-up was 2 years. We present data from exploratory analyses of pts treated with H in the first- or second-line setting who continued to receive H-based treatment at disease progression or who discontinued.
Results: A total of 623 pts were enrolled, of whom 221 and 117 received their first H regimen as first- or second-line treatment, respectively. Among pts receiving first-line H, median OS from first H treatment was longer in pts who continued to receive H compared with those who discontinued (not yet reached after 27.8 months' follow-up vs 16.8 months [95% CI: 12.5−19.5]; $p < 0.0001$). Similarly, in the first-line setting, OS at 2 years was 73.7% in pts who continued H compared with 24.7% in pts who discontinued. Median OS from the date of first progression for pts who received first-line H was 21.3 vs 4.6 months for pts who continued H compared with those who discontinued, respectively ($p < 0.0001$). Among pts receiving second-line H, median OS from the first H treatment was again longer in those who continued treatment with H after progression compared with those who discontinued (27.2 vs 15.6 months, respectively; $p = 0.076$). In addition, median OS from the date of first progression for pts who received second-line H was 15.5 vs 11 months for pts who continued H compared with those who discontinued H, respectively ($p = 0.023$).
Conclusion: Continuing H after disease progression in women with HER2-positive MBC who received H in the first- or second-line setting appears to be associated with a survival advantage.

2100 ORAL

Prediction of brain relapse (BR) in HER-2 positive metastatic breast cancer (MBC) patients (pts)

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Background: We have earlier demonstrated a high risk of BR in HER2 positive MBC pts (J Clin Oncol, 2006; 24, 18S). The present study, based on longer follow-up and increased number of events, includes extensive analysis of clinical and pathological factors determining the risk of BR in this group.
Material and Methods: Study group included 264 consecutive HER2-MBC pts aged from 24 to 77 years (median 49 years). A total of 131 pts (50%) were premenopausal, 130 (49%) – postmenopausal and 3 (2%) – with unknown menopausal status. Dominant site of disease included soft tissue (28 pts, 11%), bones (26 pts, 10%) and viscera (210 pts, 80%). A total of 210 pts (80%) were administered trastuzumab for metastatic disease, usually in combination with other systemic therapies. Statistical analysis included contingency tables, chi-square test, Kaplan-Meier survival analysis and Cox proportional hazard model.
Results: After a median follow-up of 2.8 years the clinical BR occurred in 75 pts (28%). Median time from treatment dissemination to BR was 10 months (range, 0−81 months), and the cumulative one- and two-year risk of BR was 17% and 31%, respectively. The cumulative one-year risk of BR in post- and premenopausal pts was 8% and 24%, and the two-year risk – 29% and 33%, respectively ($p = 0.019$). The cumulative one- and two-year risk of BR in pts administered trastuzumab was 11% and 25%, respectively, compared to 14% and 33%, respectively in pts who did not receive trastuzumab ($p = 0.54$). In the multivariate analysis premenopausal status (HR = 1.96; $p = 0.008$), and time to distant relapse shorter than two years (HR = 1.72; $p = 0.031$) were significantly related to the risk of BR, whereas lobular carcinoma was at borderline level (HR = 2.12, $p = 0.061$). Based on the multivariate analysis a prognostic index of the risk of BR in HER-2 positive MBC pts was developed. In the low-risk group (0−1 unfavorable variables; 68% of all pts) the cumulative one- and two-year risk of BR was 11% and 23%, respectively, compared to 28% an 46%, respectively in the high-risk group (2−3 unfavorable variables; 32% of all pts). The hazard risk of BR in the high- vs. low-risk group was 2.42 ($p < 0.001$). The median survival in pts with BR was 9 months, with 39% and 13% one- and two-year survival probability, respectively.
Conclusions: Clinical and pathological factors may select MBC patient categories with particularly high risk of BR in whom preventive strategies should be considered.

2101 ORAL

Phase III study of ixabepilone plus capecitabine in patients with metastatic breast cancer (MBC) progressing after anthracyclines and taxanes: subgroup analysis of patients receiving ixabepilone in the first-line setting

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Background: Anthracyclines and taxanes are increasingly used as adjuvant therapy in breast cancer. Patients who progress within 1 year of adjuvant taxane and anthracycline therapy have limited therapeutic options for first-line treatment in the metastatic setting. Ixabepilone, a semi-synthetic analog of epothilone B, was developed to overcome tumor resistance mechanisms. This phase-III trial evaluated ixabepilone plus capecitabine vs capecitabine alone.
Methods: 752 MBC patients resistant to anthracyclines and taxanes were randomized to ixabepilone (40 mg/m^2 iv over 3h on day 1 every 3 weeks) in combination with capecitabine (2000 mg/m^2 po in 2 divided doses, on days 1−14 of a 21-day cycle), or capecitabine alone (2500 mg/m^2 on the same schedule). Resistance was defined as disease progression within 3−4 months following anthracycline/taxane in the metastatic setting and 6−12 months following adjuvant anthracycline/taxane therapy. A prospectively-defined subset analysis was performed in patients who received ixabepilone plus capecitabine as first-line treatment after adjuvant anthracycline/taxane.

	Total population		First-line after adjuvant A/T[a]	
	Ixabepilone + capecitabine (N = 375)	Capecitabine (N = 377)	Ixabepilone + capecitabine (N = 25)	Capecitabine (N = 30)
PFS (mo), median (95% CI)	5.8 (5.5–7.0)	4.2 (3.8–4.5)	7.0 (4.5–8.8)	2.1 (1.4–4.2)
Hazard ratio (95.17% CI)	0.75 (0.64–0.88)		0.46 (0.25–0.85)	
Objective response rate (%)	35	14	44	10

A/T, anthracycline/taxane.

Results: Ixabepilone plus capecitabine was superior to capecitabine with a 40% prolongation of median progression-free survival (PFS) ($p < 0.001$). Fifty-five patients received ixabepilone plus capecitabine or capecitabine as first-line therapy. PFS was again prolonged for patients receiving