measurable disease (34.3% vs 16.4%; $p < 0.0001$). The current analysis is based on 355 events and shows that bevacizumab plus paclitaxel significantly prolongs PFS compared to paclitaxel alone (10.97 vs 6.11 months; HR = 0.498, $p < 0.001$). Early follow-up suggests that bevacizumab plus paclitaxel improves overall survival (HR = 0.674, $p = 0.01$), although data are immature.
Conclusions: First-line bevacizumab plus paclitaxel significantly prolongs disease-free survival compared to paclitaxel in patients with MBC, with minimal increase in toxicity.

276 ORAL

A Phase II multicentre uncontrolled trial of sorafenib (BAY 43–9006) in patients with metastatic breast cancer

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Background: Sorafenib (BAY 43–9006) is a novel, oral multi-kinase inhibitor that targets the Raf/MEK/ERK pathway at the level of Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR-β, thereby affecting the tumour and vasculature. In Phase I trials, single-agent sorafenib showed preliminary anti-tumour activity in patients with metastatic breast cancer. This multicentre, Phase II, open-label, single-arm study was designed to assess WHO-defined best overall response rate in patients with metastatic breast cancer, and investigate breast cancer biomarkers predicting for sorafenib sensitivity.
Patients and methods: 54 patients (ECOG PS 0–2) who had received at least one prior chemotherapy for metastatic breast cancer, and failed at least one adjuvant hormonal therapy if ER/PgR positive, and failed trastuzumab therapy if HER2 positive, received continuous oral sorafenib 400 mg bid. Patients had received between 1 and 11 prior chemotherapy regimens, and 64% received at least four prior chemotherapy treatments. The primary endpoint of the study was overall response rate. Other endpoints included time to progression (TTP), time to response, duration of response, and survival. Baseline markers in the tumour (pERK, VEGFR, HER-2, ER, PgR) and in the blood (serum EGFR, serum VEGF, serum uPA, plasma PAI-1) were collected to conduct pharmacodynamic studies. Adverse events (AEs) were graded by CTCAE v3.0.
Results: Of the 50 patients evaluable for response, one (1.9%) had a partial response, and 19 (35.2%) had stable disease. The overall median TTP was 55.5 days (range 0–280). The most common drug-related AEs were rash/desquamation (31.5% of patients), anorexia (27.8%), hand–foot skin reaction (HFS: 22.2%), pruritus (22.2%), and diarrhoea (18.5%). Frequent grade 3 events included rash/desquamation (5.6% of patients), fatigue and HFS (both 3.7%). Three patients withdrew due to AEs, 42 due to progressive disease, and two patients died during the study. There are five patients still undergoing treatment.
Conclusions: Sorafenib monotherapy was very well tolerated in this group of heavily pretreated patients. Prolonged stabilization of disease was observed in a few patients, and its association with specific tumour and/or circulating biomarkers is being investigated. Combination studies of sorafenib in breast cancer are planned.

277 ORAL

Interim results of a phase II randomized study of lapatinib (GW572016) as first-line treatment for patients with FISH-amplified advanced or metastatic breast cancer

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Background: Lapatinib is a selective, reversible, oral small molecule inhibitor of both ErbB1 (EGFR) and ErbB2 (HER-2/*neu*) kinase activity. Results of phase I and II studies in women with metastatic breast cancer (MBC) suggest activity of lapatinib in heavily pretreated patients (pts). The primary objective of this study was to evaluate the response rate of two lapatinib dosing regimens as first-line treatment for pts with locally advanced or MBC and documented ErbB2 amplification by FISH.
Material and methods: Eligible pts had advanced or MBC that amplified the ErbB2 gene and measurable disease (RECIST). Pts were not previously treated with trastuzumab in the metastatic setting, and those with any prior therapy (except hormonal treatment) for advanced or metastatic disease were excluded. Pts were randomized (1:1, open label) to lapatinib 1500 mg as a single daily dose (QD) or lapatinib 500 mg twice daily (BID). The primary endpoint was response rate at week 12, after which pts with no signs of progressive disease could choose to continue lapatinib. Response was defined by RECIST criteria. Final enrollment of 130 patients is planned; an interim analysis was scheduled after 40 patients reached 12 weeks of treatment.
Results: As of April 21, 2005, 56 patients were enrolled. Interim analysis was performed on the first 40 patients randomized to treatment (n = 19 on 500 mg BID and n = 21 on 1500 mg QD). Results indicated that 10/40 had stage IIIb or IIIc disease, 30/40 had stage IV disease, and baseline ECOG PS score was zero (n = 13) or 1 (n = 27). No unexpected toxicity was reported thus far, with no grade 3/4 treatment-related adverse events. Efficacy by dose schedule appeared comparable. By investigator review, a confirmed PR was demonstrated in 12 pts (30%), with unconfirmed PR in 3 pts (7.5%). An additional 13 pts (32.5%) had SD for at least 8 weeks. Ten pts (25%) had PD, and efficacy was unknown in 2 pts. An independent radiology review was performed in the 40 pts, demonstrating PR in 14 pts (35%), unconfirmed PR in 2 pts (5%), SD in 14 pts (35%), PD in 5 pts (12.5%), and unknown efficacy in 5 pts (12.5%).
Conclusions: Lapatinib appears well tolerated and shows evidence of activity as first-line treatment for women with FISH-amplified advanced breast cancer. These data support the emerging role of small molecule tyrosine kinase inhibitors in the treatment of pts with breast cancers exhibiting ErbB2 amplification.

278 ORAL

Phase I study of lapatinib (GW572016) in combination with trastuzumab in advanced ErbB2-positive breast cancer

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Background: Lapatinib is an oral, selective and highly potent competitive tyrosine kinase inhibitor of both ErbB1 and ErbB2. *In vitro* synergistic activity has been demonstrated between lapatinib and trastuzumab in ErbB2-positive breast cancer cell lines, and efficacy of both drugs may be enhanced via differential mechanisms of action and receptor site activity.
Material and methods: Patients (pts) with advanced or metastatic ErbB2-overexpressing breast cancer (FISH+ or IHC 2+ or 3+) were enrolled. Lapatinib was administered orally in escalating doses (750 mg-1500 mg/day) in combination with weekly standard dosing of trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly). Three pts were treated at each dose cohort, with expansion to 6 if a dose-limiting toxicity (DLT) was observed. Once optimally tolerated regimen (OTR) was determined, pharmacokinetic (PK) parameters of lapatinib and trastuzumab alone and in combination were studied. Clinical response assessments by RECIST criteria and cardiac assessments (starting at week 4 and again at week 8) were performed every 8 weeks.
Results: A total of 54 pts were enrolled in the trial: all were assessable for clinical activity, and 50 were assessed for toxicity. Median age was 53 years (range 30–80), and 49 pts had received prior trastuzumab. A median of 4 treatment periods (1 treatment period = 4 weeks) were administered (range 1–15). Toxicities included grades 1–3 diarrhea, fatigue, nausea, anorexia, and rash. No symptomatic declines in left ventricular ejection fraction (LVEF) were reported at any dose level. Six of 27 pts (22%) in the dose escalation cohort had a response (1 CR [duration 13+ mo], 5 PR [duration 2–10+ mo]), and 2 of 27 pts (7%) in the PK cohort had a PR (duration 3+-5+ mo). A total of 8 pts had SD (duration 6–8+ months).
Conclusions: Lapatinib 1000 mg/day plus standard weekly trastuzumab was determined as the OTR. The combination of lapatinib and trastuzumab showed clinical activity in this heavily pretreated ErbB2-positive advanced breast cancer population.