5074 POSTER

First-line bevacizumab (bev) plus paclitaxel (pac) combination therapy: safety findings (n = 165) from a multicentre German non-interventional study in patients with metastatic breast cancer (MBC)

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Background: Two large phase III trials, E2100 and AVADO, have shown that bev (a humanised monoclonal antibody that specifically inhibits VEGF) combined with either pac or docetaxel significantly improves progression-free survival and response rate compared with taxane monotherapy in MBC. To gain further information on the safety and efficacy of first-line bev−pac combination therapy in a broader population treated in routine clinical practice, we are conducting a multicentre non-interventional study following the introduction of bev in Germany.
Materials and Methods: Patients who have received no prior chemotherapy for their MBC are treated with bev plus pac according to the approved indication until disease progression, unacceptable toxicity or withdrawal of consent. The primary endpoint is safety. Target accrual is 1000 patients.
Results: Data are currently available for 165 enrolled patients. Baseline characteristics were: median age 56 years (range 26−78; 30% ⩾65 years); 31% disease-free interval 2%) grade ⩾3 adverse events, irrespective of relationship to bev, were leucopenia (11%/2% grade 3/4, respectively), neutropenia (5%/3%), pain (7%/0%), hypertension (6%/0%), nausea (4%/0%) and anaemia (3%/<1%). There was no grade ⩾3 proteinuria. Overall, 20 patients experienced a grade ⩾3 adverse event reported by the investigator as related to bev. There were only six grade 4 events considered related to bev: bleeding (n = 2), infection (n = 2), hepatotoxicity (n = 1) and cardiac function (n = 1). The only grade 3 bev-related adverse events in more than one patient were hypertension (2%) and venous thrombosis/embolism (2%). Other adverse events previously reported in MBC clinical trials of bevacizumab were rare (only one case each of arterial thrombosis and gastrointestinal perforation).
Conclusions: The safety profile of bev−pac combination therapy in this community-based study is broadly consistent with results of study E2100. Incidences of typical bev side effects were similar to findings from the AVADO trial. Analysis of results from a larger patient population will be available in mid 2009.
Trial ML21165 was sponsored by Roche Pharma AG, Germany.

5075 POSTER

Sunitinib plus docetaxel and trastuzumab as first-line therapy for HER2+ advanced breast cancer

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Background: Trastuzumab (T) + docetaxel (D) is a standard 1st-line treatment (tx) for HER2+ advanced breast cancer (ABC). Sunitinib (SU) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, and FLT3 with single-agent activity in previously treated ABC. In this study [NCT00372424; Pfizer], a SU/D/T combination was investigated as 1st-line tx for patients (pts) with HER2+, locally recurrent or metastatic BC.
Materials and Methods: Female pts (⩾18 yrs, ECOG PS ⩽1) with HER2+ ABC were enrolled. Starting doses were D: 75 mg/m^2, q3w, iv, day 1; T: wkly: 4 mg/kg, day 1, followed by 2 mg/kg/wk, iv or q3w: 8 mg/kg, day 1, followed by 6 mg/kg q3w, iv; SU: 37.5 mg/d, Schedule 2/1, po, day 2. The primary objective was safety. Antitumor activity and pharmacokinetics (PK) were secondary endpoints. On discontinuation of D, responsive pts (PR or SD) could continue SU + T until disease progression.
Results: As of Oct 2008, 22 pts were enrolled; 8 pts continue on study tx and 14 have discontinued (7 due to PD; 2 due to pt decision; 2 due to AEs; 2 due to global deterioration; 1 death). 22 pts were evaluable for safety and 18 for antitumor activity. 12 pts (55%) were chemo-naïve. Pts received 158/115/169 cycles of SU/D/T, respectively, with a median of 8/6/9 cycles/pt (range: 1−17/1−12/1−17). The planned dose of SU (37.5 mg/d) was reduced to 25 mg/d in 13/22 pts and was interrupted in 14/22 pts. AEs led to SU dose reductions/interruptions in 12 pts, most frequently: grade (G) 3/4 neutropenia (n = 8), G3 febrile neutropenia, G3 fatigue and G3 diarrhea (each n = 2). The most frequent non-hematologic G3 AEs were fatigue/asthenia (23%), diarrhea (14%), stomatitis (9%) and vomiting (9%). G4 AEs were transaminase increase; accidental overdose of SU; respiratory failure following T; intestinal perforation (each n = 1). 1 cardiac AE occurred (G3 supraventricular tachycardia) and transient LVEF decline was seen in 3 pts (14%). G3/4 neutropenia occurred in 19 pts, and 5 pts had febrile neutropenia. G-CSF was administered to 11 pts. Steady-state levels of SU, its metabolite, and total drug were similar to levels achieved with SU alone. Of 18 evaluable pts, 14 (78%) had confirmed PRs and 3 had SD.
Conclusions: The combination of SU/D/T, given as 1st-line tx to HER2+ pts with ABC, is feasible. AEs were manageable through dose delay/reduction and no new, unexpected AEs occurred. Preliminary evidence of antitumor activity is encouraging and warrants further evaluation.

5076 POSTER

A prospective study of vinorelbine and capecitabine combination therapy in patients with metastatic breast cancer pretreated with anthracyclines and taxanes

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Background: The purpose of this phase II study was to prospectively evaluate the feasibility of vinorelbine in combination with capecitabine in Chinese patients with metastatic breast cancer (MBC) pretreated with anthracyclines and taxanes.
Materials and Methods: Eligible patients had MBC and had previously been treated with anthracyclines and taxanes. The planned sample size was 70 patients. Vinorelbine (25 mg/m^2 intravenous infusion day 1 and day 8) and capecitabine (1000 mg/m^2 bid, 14 days on, 7 days off) were administered every 3 weeks for up to 6 cycles, until disease progression, unacceptable toxicity or patient consent withdrawal. Objective response rate was the primary endpoint and time to progression (TTP), overall survival and safety profile were the secondary endpoints.
Results: In total, 72 patients with prior anthracycline and taxane exposure were enrolled. 42 patients (58.3%) were treated in the 2nd-line setting. A total of 297 cycles of therapy were given, with a median of 4 cycles (range 2−8) per patient. In the ITT analysis, the overall response rate was 45.8% (95% CI: 34.2−57.4%), including 5 complete responses (6.9%) and 28 partial responses (38.9%). With a median follow-up of 22 months, the median TTP was 7.7 months (95% CI: 5.5−10.0 months), the median duration of response was 13.7 months (95% CI:10.1−16.4 months) and the median survival time was 26.1 months (95% CI: 19.6−32.6 months). The most common hematological adverse events were leukopenia (81.9%) and neutropenia (80.6%; G3/4 41.7%), while nausea (62.5%) was the most frequent non-hematological toxicity. Hand-foot syndrome (any grade) occurred in 12.5% of patients and diarrhea was rare.
Conclusions: Capecitabine at 1000 mg/m^2 bid combined with vinorelbine is an effective and safe treatment approach for MBC patients pretreated with anthracyclines and taxanes. This study was sponsored by Professor Binghe Xu, Cancer Institute & Hospital, Chinese Academy of Medical Sciences.

5077 POSTER

Lapatinib plus letrozole vs. letrozole alone in patients (pts) with endocrine sensitive, HER2+, previously untreated metastatic breast cancer (MBC) with multiple (>3sites) or liver metastases

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Background: EGF30008, a double-blind, placebo-controlled, phase III trial, showed that combination therapy with lapatinib and letrozole significantly

increased investigator-assessed progression free survival (PFS) over letrozole alone (8.2 vs 3.0 mo, HR = 0.71 (0.53, 0.96) P = 0.019) for women with endocrine sensitive, HER2+ (ErbB2+), previously untreated MBC. Two sub-populations within the HER2+ pt cohort were examined in retrospective analyses: presence of baseline liver metastases and ⩾3 baseline metastatic organ sites.
Methods: 1286 pts were randomized to letrozole/lapatinib or letrozole/placebo. HER2+ was defined by a positive FISH ratio (>2.0) or by immunohistochemistry 3+. Investigator-assessed PFS in these subpopulations were analyzed using Kaplan-Meier with stratified log rank to compare treatment arms within each subgroup: pts with baseline liver metastasis (n = 71) and pts with ⩾3 baseline metastatic organ sites (n = 89).
Results: Pts with HER2 amplified breast cancer who had baseline liver metastasis derived a greater PFS benefit with combination lapatinib and letrozole: 2.7 to 4.4 mo, HR = 0.39 (0.23, 0.65), P ⩽ 0.001. Combination therapy for pts with ⩾3 baseline metastatic organ sites prolonged median PFS from 2.7 to 8.0 mo, HR = 0.59 (0.37, 0.94), P = 0.015.
Conclusions: These retrospective data provide further evidence of the effectiveness (prolonged PFS) of the oral lapatinib/letrozole combination in HER2 amplified, endocrine sensitive metastatic tumors in pts with visceral burden or higher number of metastases.

5078 POSTER

Treatment of leptomeningeal involvement of breast cancer with high-dose methotrexate and ifosfamide

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Background: Leptomeningeal spread in solid tumors has a poor prognosis. Intrathecal chemotherapy and radiation are symptomatic therapeutic approaches. Systemic chemotherapy with blood-brain-barrier crossing agents might be beneficial regarding its potential to treat concomitant brain metastases and systemic disease. In a pilot trial we treated patients with meningeal spread of breast cancer (BC) with high-dose methotrexate and ifosfamide (HDMTX/IFO).
Methods: From July 2007 all consecutive BC patients with leptomeningeal involvement and creatinine clearance >50 ml/min have been treated with 4 g/m^2 MTX as a 4 h infusion on day 1 (with dose adjustment for creatinine clearance and leucovorine rescue starting after 24 hours) and 1.5 g/m^2/day IFO as a 3 h infusion on days 3−5. Treatment was continued for a maximum of 8 cycles.
Results: Three female patients aged 59, 62 and 65 years have been treated thus far. All had concomitant systemic metastases (bone and liver), two patients had been pretreated with up to four systemic chemotherapy regimens. Presenting symptoms were hemi- and paraparesis, radicular pain and multiple cranial nerve palsies. In the first patient chemotherapy was stopped after two cycles due to renal toxicity CTC 2º. She remained neurologically stable for 1.5 months and then received intrathecal chemotherapy followed by six cycles of systemic chemotherapy with topotecan and ifosfamide. She was neurologically improved eleven months after start of HDMTX/IFO. Two patients received six and seven cycles chemotherapy and markedly improved neurologically with stable systemic disease. Time to neurological progression was 5.5 and 7.0 months and overall survival was 8.3 and 11.0 months, respectively.
Further grade 3 or 4 toxicities were thrombopenia 3º in one and leucopenia 3º in two patients.
Conclusion: Systemic chemotherapy with HDMTX/IFO is feasible and active in leptomeningeal involvement of BC. Further improvement may be achieved by additional intrathecal therapy. Liposomal cytarabine has demonstrated impressive activity in malignant leptomeningeal disease. Therefore we initiated a multicenter phase II trail combining systemic HDMTX/IFO and intrathecal liposomal cytarabine in BC patients with meningeal +/− brain relapse.

5079 POSTER

Role of paclitaxel in neoadjuvant chemotherapy in stage IIA-IIIA breast cancer

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Background: Neoadjuvant chemotherapy with doxorubicine and cyclophosphamide in **stage IIA-IIIA** breast cancer has a proven importance. In order to analyze the impact of adding paclitaxel to this regimen, a prospective study was designed in 2004.
Methods: The studied lot consisted in 124 patients admitted in the Oncology Clinic of Craiova, Romania between February 2004 and March 2009. The most important eligibility criteria were: stage IIA-IIIA breast carcinoma, her-2/neu negative, measurable disease and an ECOG performance status of 0 or 1. Patients were randomized 1:1 in order to receive the standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm;) – group A, or paclitaxel plus standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm and paclitaxel 200 mg/sqm;) – group B. Both regimens were administered in cycles repeated every 21 days. If partial response occurred after 2 cycles, patients undertook surgical treatment without further chemotherapy; if not, they were administered a total of 4 cycles, followed by surgery. Stratification criteria were: age, staging, involvement of axillary lymph nodes and hormonal receptors status. Primary endpoints of the study were the response rate for each arm of the study and the quality of life in each group; the latter was assessed using a specific questionnaire.
Results: 124 patients were randomized between February 2004 and March 2006: 62 in group A and 62 in group B. The groups were well balanced regarding the stratification criteria. A significant difference was found between response rates in the 2 groups: partial response rates were 64.51% in group B compared to only 51.62% in group A, while complete response occurred only in group B (1.61%). The remainder of the patients had stationary disease after the regimens: 33.87% of group A and 48.39% of group B. The odds ratio for developing a partial response after the triple association regimen compared to the double association one was 1.25:1. We observed significant toxicities for triple association regimen when compared with standard regime: 34% of grade 3 neutropenia versus 15% and 15% peripheral neuropathy versus 3%.
Conclusions: Despite the higher incidence of neutropenia in the triple association regimen, the higher response rate recommends it as neoadjuvant chemotherapy for stage IIA-IIIA breast cancer.

5080 POSTER

Safety and tolerability of fulvestrant high-dose (500 mg) in postmenopausal women with hormone receptor positive advanced breast cancer

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Background: Two open-label, multicenter Phase II trials, NEWEST (9238IL/0065) and FIRST (9238IL/0006), have shown improved biological and clinical efficacy with fulvestrant high-dose regimen (HD; 500 mg/month + 500 mg on day 14 of month 1) compared with fulvestrant approved-dose (AD, 250 mg/month) and anastrozole, respectively, in either the neoadjuvant and first-line setting in women with hormone receptor-positive advanced breast cancer. Here, safety and tolerability data are presented.
Material and Methods: NEWEST: 211 patients were randomised to fulvestrant HD (n = 109) or AD (n = 102) for 16 weeks prior to curative surgery. At 16 weeks, AEs, endometrial thickness, and serum bone markers were compared with baseline-data. FIRST: 205 patients were randomised to fulvestrant HD (n = 102) or anastrozole (n = 103) as first-line therapy until progression or withdrawal due to an AE.
Results: NEWEST: Incidence rates for any AE (irrespective of causality) were comparable in both groups (72.9% for fulvestrant HD vs. 69.3% for fulvestrant AD), with injection site pain being most common within the HD-group and hot flashes within the AD-group. SAEs other than death occurred in 13.1% in the HD-group and in 11.9% in the AD-group; 0.9% vs. 3% were judged as treatment-related. AEs leading to withdrawal of treatment were rare (0.9% for fulvestrant HD vs. 1% for fulvestrant AD). No adverse effects on endometrial thickness or serum bone markers were identified in either group. FIRST: Incidence rates for any AE were comparable in both groups (70.3% vs. 69.9%) as were incidence rates for drug-related AEs (29.7% for fulvestrant HD vs. 28.2% for anastrozole). Among drug-related AEs, hot flashes were most common in both groups (7.9% vs. 12.6%). SAEs were rare in both study groups (11.9% vs. 9.7%), including only one patient in the fulvestrant HD group with a drug-related SAE (hypertension). Three patients in each group (3.0% vs. 2.9%) experienced an AE leading to discontinuation of treatment.
Conclusions: The safety profile of fulvestrant HD is comparable with that of fulvestrant AD and anastrozole. Fulvestrant HD was well tolerated and