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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.

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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.

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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.

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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