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Efficacy of combined Trastuzumab and CMF therapy in women with metastatic breast cancer. EORTC protocol 10995

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Background: Efficacy of classical CMF combined with 3-weekly Trastuzumab (T), followed by T alone in metastatic breast cancer (MBC).
Materials and Methods: Patients (pts) with previously treated MBC were enrolled into a Phase II study of T (4 mg/kg then by 2 mg/kg) IV weekly plus CMF, Bonadonna regimen, for a maximum of 8 cycles (cy), followed by T alone (6 mg/kg) IV 3 weekly. Primary objective was the incidence of congestive heart failure and response rate (RR) of the combination of T+CMF. Entry criteria included HER2 overexpression, limited anthracycline (A) exposure, normal baseline LVEF and measurable disease (RECIST).
Results: The trial was closed to recruitment in January 2006, 10 pts are still on treatment. Seventy one pts were entered with a median age of 54 (range 31−75). Forty-one pts had prior CT (32 A), of which 26 adjuvant, 6 MBC, and 9 both adjuvant and MBC. Adjuvant CMF was given in 14 pts. Median PS was 0, 52 pts had visceral disease with a median interval from diagnosis to first relapse of 33.4 months (mo). Out of 70 pts receiving T+CMF (34 pts with 8 cy), 42 continued with T alone for a median duration of 7 cy. Eleven pts discontinued treatment due to toxicity (9 on T+CMF, 2 on T alone). To date, the RR is 54% (32/59 pts): 55% (24/44) 1st line; 53% (8/15) 2nd line. Among pts receiving prior adjuvant CMF, the RR was 6/14 (43%). An independent review of responses is underway. Median time to response was 2 mo, median duration of response was 8.2 mo, with 63% of responders having a remission for more than 6 mo, and a maximum duration of 1.3 yrs in 2 pts. The median progression free survival was 9.5 mo.
Conclusions: Combination of T+CMF regimen is feasible treatment for patients with HER2 positive MBC. Preliminary response data indicate good efficacy of CMF+T in MBC patients.

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MO19391: an open-label safety study of bevacizumab plus taxane monotherapy or in combination as first-line treatment of patients with locally recurrent or metastatic breast cancer (LR or MBC)

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Background: In randomised phase III trial E2100, the addition of bevacizumab to first-line paclitaxel significantly improved progression-free survival in patients with LR or MBC. The MO19391 trial is investigating the safety profile of bevacizumab in LR or MBC in combination with standard first-line taxane therapy. It will also form the basis of a second-line duration trial after progressive disease (PD).
Methods: This open-label, single-arm trial will enrol approximately 2,300 patients from around 510 centres in 50 countries worldwide. The primary endpoint is to assess the safety of first-line bevacizumab plus taxane-based therapy in the treatment of LR or MBC. Secondary endpoints include TTP and OS. Patients must have histologically confirmed, HER2-negative LR or MBC and ECOG PS 0−2. Exclusion criteria include prior chemotherapy for LR or MBC and evidence of CNS metastases. Patients receive bevacizumab (10 mg/kg q2w or 15 mg/kg q3w) in combination with the physician's choice of taxane regimen (or investigator's standard of care [SOC] regimen if taxanes are contraindicated or not SOC of the investigator, although anthracyclines are not permitted). Treatment continues until disease progression or unacceptable toxicity. Patients showing PD will be offered randomisation into a trial testing second-line chemotherapy +/− bevacizumab. All serious and non-serious adverse events that occur will be collected, along with additional information regarding adverse events of special interest (hypertension, proteinuria, wound-healing complications, arterial and venous thromboembolic events, CNS bleeding, other haemorrhages, GI perforations and congestive heart failure).

	ITT population (n = 177)
Median age (years)	52
range	29–76
ECOG PS (%)	
0	57.4
1	33.0
2	9.7
ER status (%)	
+	64.7
−	33.8
unknown	1.4
PR status (%)	
+	55.4
–	39.6
unknown	5.0
Disease stage (%)	
LR	1.7
MBC	98.3
Neo/adjuvant chemotherapy (%)	
yes	83.3
no	16.7
Neo/adjuvant anthracycline (%)	
epirubicin	42.7
doxorubicin	48.2
Neo/adjuvant taxane (%)	
paclitaxel	15.5
docetaxel	20.0
Chemotherapy backbone (%)	
taxane monotherapy	64.4
taxane combination	24.9
other	10.2

Results: Recruitment commenced in 09/06. As of 03/07, 283 patients have been enrolled, from 20 countries. Patient characteristics for the ITT population are presented in the table.
Conclusions: MO19391 is a large ongoing trial that will further elucidate the safety profile of bevacizumab in a community setting. Analysis of safety will be presented.

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Triple combination of oral vinorelbine, capecitabine and trastuzumab as first-line treatment in HER2-positive metastatic breast cancer (MBC): latest results of an international phase II trial

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Background: Chemotherapy (CT) plus trastuzumab (H) is the standard first-line treatment for HER2-positive MBC. H plus vinorelbine is an active and well-tolerated regimen in this setting. The all-oral combination of oral vinorelbine (NVBo) and capecitabine (X) also appears active and well tolerated in MBC. For the first time, we report efficacy and safety results from the full population of 50 patients (pts) entered in an international trial evaluating the NVBo + X + H combination in HER2-positive MBC.
Materials and Methods: In this multicentre trial, main eligibility criteria included: HER2-positive disease (IHC 3+ or FISH+), documented measurable MBC previously untreated by CT, relapse 6 months after completing neoadjuvant or adjuvant CT, Karnofsky PS $\geqslant$70, age $\geqslant$18 years.

Pts received 3-weekly cycles of NVBo 80 mg/m^2 (after a first cycle at 60 mg/m^2 in the absence of G3/4 neutropenia) days 1 and 8; X 1000 mg/m^2 bid (750 if ⩾65 years) days 1−14; H 4 mg/kg day 1 as a loading dose then 2 mg/kg i.v. weekly starting on day 8. Treatment was continued until progression or unacceptable toxicity.
Results: Baseline characteristics: median age 53.5 years (18% ⩾65); prior (neo)adjuvant CT in 54%; type of CT: anthracycline 55%, anthracycline + taxane 30%, CMF 11%, taxane 4%; visceral involvement in 82%, >2 metastatic sites in 34%. Treatment administered: median 9 cycles, median relative dose intensity: NVBo 75%, X 77%, H 96%; NVBo dose escalation to 80 mg/m^2 in 87% of pts. Safety (n = 50, G3/4 NCI CTC v2 adverse events): neutropenia 69% of pts, hand–foot syndrome 18%, diarrhoea 16%, vomiting 12%, febrile neutropenia 8%, asthenia 8%, infection with G3/4 neutropenia 4%, LVEF decline 4%, stomatitis 4%. Efficacy (n = 46 evaluable pts): objective response (OR) rate (RECIST) 74% (95% CI [59−86]), CR 13%, PR 61%, SD 20%, PD 6%. OR for visceral metastases: 68%. Disease control (CR+PR+ SD for ⩾6 months) 91%. After a median follow-up of 17.6 months, median progression-free survival and overall survival have not been reached. 12 patients are still receiving treatment.
Conclusions: NVBo + X is an effective first-line chemotherapy option in combination with H in pts with HER2-positive MBC, with an acceptable safety profile.

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Phase I-II study of IV vinorelbine (VRL) and oxaliplatin (OXP) every two weeks (q2w) in metastatic breast cancer (MBC): Interim results of the phase II trial

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Background: The combination of VRL and OXP was shown to be effective for the treatment of NSCLC. We designed a scheme for first line MBC consisting of administering IV VRL and OXP q2w to determine the maximal tolerated dose (MTD), recommended doses (RDs) and safety. The phase II part was planned to confirm the clinical efficacy and safety of the combination.
Materials: 30 chemonaive patients (pts) with MBC were accrued in the phase II part of the study (recruitment still ongoing). As previously reported for the phase I part, RDs consisted of VRL 30 mg/m^2 with OXP 90 mg/m^2 both administered every 2 weeks.
Results: Median age 58 y (range; 33−83), 24 pts (80%) received prior (neo)adjuvant CT. Karnofsky performance status 100%, 63%; 90%, 29.6%; 80%, 7.4%. Sites of metastasis included liver (33.3%), lung (44.3%), bone (46.7%), soft tissue (13.3%). Local relapse in 8 pts (26.6%). 2 pt were not evaluable for efficacy. Among the 28 pts evaluable, 20 pts achieved objective responses (OR 71.4%, 95% CI, 51.3% to 86.8%) among them 14.3% with complete response; 17.9% pts had a stable disease and 10.7% presented progressive disease. With a median follow up of 4 months (range 1.2−11.9), median survival has yet to be reached. All patients were evaluable for safety. A total of 207 cycles (cy) were administered. This regimen was well tolerated with neutropenia WHO grade 3−4 observed in 11% cy (40% pts). Non-hematological toxicity was mild and manageable, with fatigue grade 3 reported in 6 cy (3 pts), constipation grade 3 in 2 cy (1 pt) and neurotoxicity grade 3 in 2 cy (2 pt).
Conclusions: The combination of VRL and OXP as first-line treatment is a highly active, well-tolerated and convenient regimen in pts with MBC.

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Activity of fulvestrant in patients with visceral metastases: result from EFECT

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Background: Patients with visceral metastases are often regarded as being less likely to respond to hormonal therapy than those without visceral metastases.
Methods: EFECT is a randomised, double-blind, double-dummy, multicentre, Phase III trial, comparing the efficacy and tolerability of fulvestrant (Faslodex®) vs exemestane (Aromasin®) in postmenopausal women with hormone receptor-positive advanced breast cancer (ABC) progressing/recurring after prior non-steroidal aromatase inhibitor (AI) therapy. Fulvestrant (IM) was used in a loading-dose regimen: 500 mg on Day 0, 250 mg on Days 14 and 28, and 250 mg every 28±3 days thereafter. Exemestane 25 mg PO was given once daily.
Results: The overall analysis from EFECT demonstrated the effectiveness of fulvestrant vs exemestane in this trial population. Overall, 693 women were randomised to fulvestrant (n = 351) or exemestane (n = 342). Of these, 56.1% of patients receiving fulvestrant and 57.9% of patients receiving exemestane had visceral involvement (lung and/or liver). Here, efficacy data from EFECT were analysed in evaluable patients with and without visceral metastases.

	Fulvestrant		Exemestane	
	VM	No VM	VM	No VM
Objective response, %	7.1	8.0	4.4	11.6
Clinical benefit, %	29.1	38.6	27.2	40.7
Median time to progression, months	3.1	4.1	2.8	5.2
Median duration of clinical benefit[a], months	9.9	8.0	8.1	8.6

[a]Retrospective analysis; VM, visceral metastases.

Conclusion: In EFECT, both fulvestrant and exemestane demonstrated clinical benefit in patients with visceral metastases. This builds on similar Phase III data for fulvestrant in the post-tamoxifen setting.

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Activity of Fulvestrant in patients with HER2-positive advanced breast cancer

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Background: Although endocrine therapy is commonly used to treat advanced breast cancer (ABC), patients with HER2-positive (HER2+) disease are generally regarded as being less responsive to such treatments. Fulvestrant (FaslodexTM), a novel estrogen receptor (ER) antagonist with no agonist effects, is licensed for the treatment of postmenopausal women with ABC after progression on prior chemotherapy. Here we examine pooled clinical experience data from patients with HER2+ disease who received fulvestrant treatment.
Methods: Postmenopausal women with HER2+ disease were treated with fulvestrant 250 mg/month IM until progression or another reason for discontinuation. Clinical response was assessed monthly using RECIST or UICC criteria, or the clinical judgment of the treating physician. Clinical benefit (CB) was defined as the proportion of patients experiencing a response (complete response [CR] or partial response [PR]) or stable disease (SD) lasting ⩾6 months.
Results: Seventy patients with HER2+ ABC and a median age of 61 years (range 30−85 years) received fulvestrant. Patients had received a median of 2 prior endocrine therapies (range 0−3) and 2 chemotherapies (range 0−4) for ABC. ER and/or progesterone receptor (PgR) status was assessed in 69 patients. Twenty-eight patients experienced CB (5 PR and 23 SD ⩾6 months) with fulvestrant, giving a CB rate of 40.0%, with activity noted up to the fourth line of endocrine therapy, and the seventh line of overall ABC therapy. The CB rate was 44.4% in ER+/PgR+ patients (n = 36) and 43.5% in ER+/PgR− patients (n = 23).
Conclusion: From these data, fulvestrant appears to demonstrate activity in patients with HER2+ ER+ ABC. The observed activity was independent of PgR status and was consistent with the efficacy of fulvestrant seen in the overall ABC population. These are encouraging data, warranting further exploration of the use of fulvestrant in treating HER2+ disease.