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High efficacy of the combination of oral vinorelbine (NVBo), capecitabine (X) and trastuzumab (H) in HER2-positive metastatic breast cancer (MBC): updated results of an international phase II trial with a median follow-up of 39 months

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Background: Chemotherapy (CT) plus H is the standard treatment for HER2-positive MBC. H plus vinorelbine combination therapy is an active and safe regimen in the first-line setting. The all-oral CT combination of NVBo and X has shown activity and good tolerability in MBC. We report the latest results from a multinational phase II study assessing the efficacy and safety of NVBo, X and H in HER2-positive MBC after a median follow-up of 39 months.
Materials and Methods: In this multicenter trial, main eligibility criteria included: HER2-positive disease (3+ IHC or FISH+), documented measurable metastatic disease previously untreated by CT, relapse $\geqslant$6 months after the end of neoadjuvant or adjuvant CT, Karnofsky PS $\geqslant$70. NVBo was given as a 60 mg/m^2 (cycle 1) or 80 mg/m^2 (from cycle 2) dose D1 & D8 every 3 weeks, X at 1000 (750 if $\geqslant$65 y) mg/m^2/bid D1-D14 every 3 weeks, H at 4 mg/kg on D1 as a loading dose then 2 mg/kg i.v. weekly starting on D8. Treatment was continued until progression.
Results: Main patient (pt) characteristics in the full population (n = 50): median age: 53.5 years (18% $\geqslant$65); prior (neo)adjuvant CT 27 pts (54%); visceral involvement 41 pts (82%), >2 metastatic sites 17 pts (34%); median number of cycles: 10 (range:1−71); 72% of pts received more than 6 cycles, 58% more than 8 cycles and 32% more than 16 cycles; median number of NVBo administrations: 20 (range:1–141); median number of trastuzumab administrations: 30 (range:1–218); median relative dose intensity: NVBo 76%, X 78%, H 96%; NVBo dose escalation to 80 mg/m^2: 84%. G3/4 NCI CTC v2 adverse events: neutropenia 71%, hand-foot syndrome 20%, diarrhoea 16%, vomiting 12%, asthenia 8%, febrile neutropenia 8%, infection 6%, LVEF decline 4%, stomatitis 4%, nausea 4%, alopecia (grade 2) 14%. Efficacy (n = 44 evaluable patients): objective response rate (RECIST) 77% (95% CI [62−89]), CR 21%, PR 57%, SD 18%, PD 5%, disease control (CR+PR+SD $\geqslant$6 months) 93% (95% CI [81−99]); median duration of response was 13.3 months (95% CI [9.8−15.7]) and median progression-free survival was 12.8 months (95% CI [10.8−16.9]). With a median follow-up of 39 months, overall survival results are not mature yet. 5 patients are still receiving full study treatment.
Conclusion: Combination chemotherapy with NVBo and X plus H is an active first-line regimen for HER2-positive MBC. Treatment could be continued until disease progression without a pre-planned maximum number of cycles in many patients.

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Influence of zoledronic acid on bone mineral density in premenopausal women with hormone receptor positive or negative breast cancer and neoadjuvant or adjuvant chemotherapy or endocrine treatment

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Background: Depending on baseline bone mineral density (BMD), adjuvant chemotherapy or endocrine therapy of premenopausal breast cancer patients can lead to a substantially decrease in BMD and consequently increased risk of osteoporotic fractures. Hereby, a significant decrease of BMD > 10% after 2 years of therapy has been reported. Adjuvant therapy with zoledronic acid in early breast cancer was investigated in the ABCSG-12 and the Zo-Fast trial. Zoledronic acid 4 mg given every six months increased BMD in premenopausal and postmenopausal women receiving endocrine treatment. In addition, a significant increase in PFS could be observed in favor of zoledronic acid.
Material and Methods: The goal of the two monocentric, placebo-controlled, randomized studies Probone I and Probone II is to investigates the influence of adjuvant zoledronic acid therapy on BMD in premenopausal women with BC. Hormone receptor negative patients (Probone I) are treated with (neo)adjuvant chemotherapy, hormone receptor positive patients (Probone II) with endocrine treatment alone or in combination with (neo)adjuvant chemotherapy. Patients receive zoledronic acid or placebo i.v. every 3 months for 2 years. Primary objective is the change in BMD at the lumbar spine between baseline and month 24 (measured by DXA). Secondary objectives include disease free survival, BMD at total hip and os calcis, BMD measured by QUS at os calcis and phalanges, markers of bone turnover, pathologic fractures, safety and tolerability. BMD is measured at baseline, 12 and 24 months. QUS and markers of bone turnover are measured at baseline, 3, 6, 12 and 24 months.
Results: As of April 2009, 65 hormone receptor positive and 11 hormone receptor negative patients have been enrolled into the studies. 30 out of 74 patients have already finished treatment. The design of the study and demographic data of the enrolled patients will be presented.
Conclusion: Probone I/II are two ongoing studies to evaluate the effect of adjuvant zoledronic acid on BMD in premenopausal patients with breast cancer receiving chemotherapy and/or endocrine therapy. The results of these studies will be of great interest for clinical practice because of the lack of approved treatments for the prevention of cancer treatment induced bone loss (CTIBL) in patients with early breast cancer.

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Efficacy of combination treatment with epirubicin (EPI) plus docetaxel (DOC) in advanced breast cancer

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Background: The present study aimed at evaluating whether this new regimen could be effective in patients with primary advanced breast cancer.
Material and Methods: Thirty-two women (mean age 50.4 years, range 31−63) with primary advanced breast cancer were given epirubicin (EPI) 40−60 mg/m^2 and docetaxel (DOC) 50−60 mg/m^2 intravenously every three weeks. The efficacy was evaluated after 4 cycle treatments.
Results: There were 5 complete responses (CR) and 15 partial responses (PR), giving an overall response rate of 62.5%. There were 2 pathological CR (8.0%) which showed complete disappearance of cancer cells. The high dose group showed a better response than the low-dose group. The most common grade 3/4 adverse events were neutropenia (31.3%) and general fatigue (6.0%). The 5-year survival rate in stage IIIB (n = 9) and stage IV (n = 8) patients was 46.7%. When divided into subgroups according to response (RECIST), the median survival time (MST) was 64.4 months in the responder group (CR and PR) versus 23.3 months in the non-responder group (SD and PD) ($p < 0.05$).
Conclusions: The simutaneous combination treatment of EPI and DOC is effective for primary chemotherapy and can be performed safely for outpatients.

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Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first-line therapy for HER2-negative locally recurrent or metastatic breast cancer (LR/MBC): the CECOG phase III TURANDOT trial

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Background: Bev combined with taxane-based therapy or X significantly improves progression-free survival (PFS) versus chemotherapy (CT) alone as first-line treatment for LR/MBC. However, the relative efficacy of Bev+X versus Bev+Pac is unknown.
Materials and Methods: Eligible patients (pts) have HER2-negative LR/MBC, ECOG PS 0−2 and have received no prior CT for LR/MBC.

Prior (neo)adjuvant CT is permitted if completed ⩾6 months before randomisation (⩾12 months for taxane-containing therapy). Pts receive either Bev+X (21 d cycles: X 1000 mg/m^2 bid d1−14 + Bev 15 mg/kg d1) or Bev+Pac (28 d cycles: Pac 90 mg/m^2 d1, 8, 15 + Bev 10 mg/kg d1, 15). In both arms, treatment is continued until progressive disease (PD), unacceptable toxicity or withdrawal of consent. If one agent is discontinued before PD, the other is continued. The primary objective is to demonstrate non-inferior overall survival with Bev+X versus Bev+Pac (upper limit ⩽1.33 for the 2-sided confidence interval for hazard ratio). Secondary objectives include comparison of overall response rate (RECIST), PFS, time to response, duration of response, time to treatment failure, safety (CTCAE v3) and QoL (EORTC QLQ-30). The recruitment target is 560 pts within 18 months. Assuming 12.5% dropout, a sample size of 490 eligible pts provides 80% power to reject the null-hypothesis of inferiority, assuming 24-month median overall survival with Bev+Pac.

Results: By 31st March 2009, 84 pts from 8 countries had been randomised.

	Bev+X (n = 45)	Bev+Pac (n = 39)
Median age, years (range)	61 (35−77)	60 (36−84)
Post menopausal, n (%)	39 (87)	31 (79)
ECOG PS, n (%)		
0	33 (73)	31 (79)
1	12 (27)	5 (13)
2	0	3 (8)
Stage, n (%)		
I	6 (13)	3 (8)
II	19 (42)	9 (23)
III	11 (25)	11 (28)
IV	9 (20)	13 (33)
n/a	0	3 (8)
ER negative, n (%)	14 (31)	9 (23)
PgR negative, n (%)	15 (33)	13 (33)
Metastatic sites, n (%)		
Liver	16 (36)	15 (38)
Lung	25 (56)	16 (41)
Lymph nodes	24 (53)	21 (54)
Bone	20 (44)	16 (41)
Endocrine therapy, n (%)		
Adjuvant only	18 (40)	15 (38)
LR/MBC only	5 (11)	4 (10)
Both	2 (4)	3 (8)
Adjuvant CT, n (%)	27 (60)	22 (56)
Anthracycline and taxane	6 (13)	4 (10)
Anthracycline, no taxane	18 (40)	14 (36)
Taxane, no anthracycline	0	2 (5)
Other	3 (7)	2 (5)
Mean DFI, months*	59	56

*Excluding 22 pts with primary metastatic disease.

Conclusions: This is the first trial designed to compare two different Bev-containing regimens in LR/MBC. A planned interim safety analysis will be performed when 150 eligible pts have completed 2 cycles of therapy. Updated information will be presented. Trial NCT00600340 is sponsored by CECOG.

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Epoetin beta therapy in anaemic breast cancer patients receiving chemotherapy: results of a subgroup from a large prospective cohort study

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Background: Anaemia is the most frequent haematological complication in cancer patients (Pts) receiving chemotherapy (CT). Epoetin beta (E) is an Erythropoiesis Stimulating Agent (ESA) approved for the treatment of symptomatic anaemia in adult Pts with non-myeloid malignancies receiving CT. This study is addressing the daily practice of E in anaemic cancer Pts receiving CT and was conducted to assess E use, efficacy, safety and impact on quality of life (QoL).

Material and Methods: This is an analysis of a subgroup (breast cancer Pts) from a large (n = 3265) prospective, multicentric, observational French study in oncology. Eligible Pts were 18 yrs or older, received CT for a solid tumour or a non myeloid haematological malignancy, and treated with E for anaemia. Pts were enrolled between Dec. 2004 and Mar. 2006. Planned follow-up was 4 months. Response to E (i.e. Hb increase of ⩾2 g/dl and/or an achievement of Hb level ⩾12 g/dl without any blood transfusion after E treatment initiation) was the primary endpoint. Data on treatment administration, QoL (FACT-F subscale), transfusions, safety were collected.

Results: 420 Pts with breast cancer were enrolled. Baseline characteristics in this subgroup (mean±SD): age 57.2±11.9 yrs, weight 64.3±13.8 kg, Hb level 10.2±1.0 g/dl. WHO PS 0 (18%), 1 (50%), ⩾2 (32%). Baseline Hb (g/dl): <9 (13.4%), [9−11[(64.4%), [11−12[(21%), ⩾12 (1.2%). Presenting stages were III-IV in 46% of Pts. Median time from initial diagnosis to inclusion: 22.1 months. Pts received first line (43.4%), second line (20.9%), third line or more (35.7%) CT. PolyCT was administered in 72.4% of the Pts: taxanes (42%), anthracyclins (45.1%), platinum-based CT (8.3%), targeted therapy (13.4%). At inclusion, prior radiotherapy was given in 54.1%, prior ESA in 13.9% and iron supplementation in 42.3% (1.9% intravenously). Almost all Pts (99.5%) were treated on a once weekly E regimen at a median starting dose of 30.000 IU, i.e. about 450 UI/kg. Response rate to E was 63.3% at the end of the study [95%CI: 58.1−68.2]. Mean FACT-F score improved from 27.1±11.3 at inclusion [95%CI: 25.6−28.6] to 33.5±10.5 at the end of study [95%CI: 32.1−34.9]. Only 15.2% of Pts required red blood cell transfusions. Epoetin beta was well tolerated. Thromboembolic events were reported only in 5 pts (1.3%).

Conclusions: This study conducted in routine practice confirms that epoetin beta is effective and well-tolerated to treat CT-induced anaemia in breast cancer Pts.

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Comparable efficacy of low-dose (1,000 mg/m^2 b.i.d.) capecitabine and standard-dose (1,250 mg/m^2 b.i.d.) capecitabine administered for ⩾6 weeks in older women with advanced breast cancer

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Background: Capecitabine (X) is a tumour activated oral fluoropyrimidine that generates 5-FU preferentially in tumour tissue. In patients with metastatic breast cancer, X has demonstrated consistently high efficacy with a favourable safety profile. This phase II, open-label, single-centre, sequential study (M66106) evaluated the safety and efficacy of X in older women with advanced breast cancer (ABC).

Methods: Patients were aged ⩾65 years, had a confirmed diagnosis of ABC, with measureable or evaluable disease in at least one non-irradiated site, ECOG performance status 0−2, a life expectancy ⩾3 months and adequate bone marrow, renal and hepatic function. Patients were previously untreated or had received ⩽1 prior chemotherapy and/or ⩽2 hormonal regimens for metastatic disease. Previous 5-FU-based chemotherapy was only permitted if completed ⩾1 year before study enrolment. X was initially administered at a standard dose of 1,250 mg/m^2 b.i.d. on days 1−14 every 21 days, with the treatment cycle repeated at least once. Due to the poor tolerability of standard-dose X in this population, the starting dose of X for all patients enrolled after 27 October 2000 was reduced to 1,000 mg/m^2 b.i.d. (low-dose X). The primary study endpoint was tolerability, while secondary endpoints included response rate and time to disease progression (TTP). Tumour assessments (WHO criteria) were made at 6-weekly intervals and at study withdrawal. Safety and efficacy data for the ITT population (all patients who received ⩾1 course of study treatment) have been published previously [Bajetta et al. JCO 2005;23:2155−61]. Here we report efficacy results for the standard population (all patients who received ⩾6 weeks of X at ⩾50% of the planned dose).

	Low-dose X (1,000 mg/m^2 b.i.d.) [n = 38]	Standard-dose X (1,250 mg/m^2 b.i.d.) [n = 24]
Complete response, n (%)	1 (3)	1 (4)
Partial response, n (%)	15 (39)	12 (50)
Progressive disease, n (%)	1 (3)	1 (4)
Stable disease, n (%)	21 (55)	10 (42)
Median TTP, days (range)	151 (64–244)	140 (46–252)