INTERNATIONAL BREAST CANCER STUDY GROUP IBCSG 54-16

METEORA-II

A randomized phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel as first-line or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer

MEtronomic TrEatment Option in advanced bReast cAncer: the METEORA-II trial

EudraCT number: **2016-002200-39**

Sponsor: **International Breast Cancer Study Group (IBCSG)**

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Version 1.0

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Protocol Signature Page

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Principal Investigator Protocol Signature Page

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I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide a copy of the protocol furnished to me by IBCSG, **to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed** regarding the drugs and the conduct of the trial. I agree to keep records on all patient information (Case Report Forms and patient's Informed Consent statement), and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator:_____

_____ _____

Signature Date

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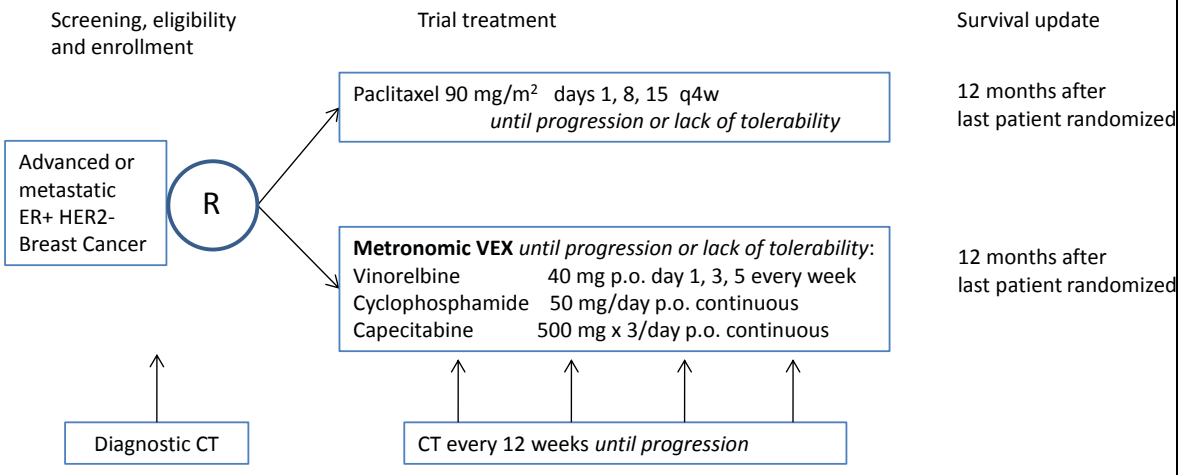
Appendices

1. Protocol Summary and Schema

Title	A randomized phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel as first- or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer
Sponsor	IBCSG
Clinical Phase	Randomized Phase II
Patient population	Patients with ER-positive/HER2-negative advanced or metastatic breast cancer
Treatment	Patients will be randomized in a 1:1 fashion to Arm A: Paclitaxel 90 mg/m^2 days 1, 8, 15 q4w Arm B: Cyclophosphamide 50 mg orally once daily Capecitabine 500 mg, orally 3 times a day (1500 mg/day) Vinorelbine 40 mg orally days 1, 3, 5 each week Patients will continue to receive assigned treatment until objective progressive disease (PD), symptomatic deterioration, unacceptable toxicity, death, or refusal to continue treatment, whichever occurs first. Patients showing RECIST 1.1 - defined PD can continue with trial treatment at the discretion of the Investigator as long as that is considered to be in the best interest of the patient and no new anticancer treatment is initiated. Patients discontinuing the active treatment will enter a follow-up phase to document first progression and survival.
Trial Schema	
Background and rationale	Breast cancer (BC) is the most common form of malignant tumor in women worldwide and incidence rates are as high as 99.4 per 100,000 women. Prognosis for patients with locally advanced or metastatic disease (ABC) remains poor, with a median survival

	of 2–4 years. About 10% of newly diagnosed BC patients present with ABC, and 30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease. In the first-line treatment of HER2 negative ABC patients, various chemotherapy regimens can be used including **taxanes,** which are among the most active agents in BC. Single agent response rates range from 20 to 50% [Eniu A, 2005]. However, eventually all patients will progress with a median time to progression of 5 to 7 months. As an example of the single agent response rates, in the recent E2100 [Miller K, 2007] and AVADO [Miles DW, 2010] randomized phase III trials in first-line HER2-negative ABC, the response rates were 22% and 46% and median progression free survival (PFS) was 5.8 and 8.1 months, respectively for the **paclitaxel** and docetaxel control arms. A weekly (qw) over a three-weekly (q3w) administration schedule of paclitaxel has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy [Seidman AD, 2008; Sparano JA, 2008]. The median time to treatment failure (TTF) for docetaxel was investigated in patients previously treated with anthracyclines (47.6% pretreated) and ranged between 2.9 months and 5.2 months [Ando M, 2001]. Weekly docetaxel showed 4.1 months of TTF in a subsequent trial [Tabernero J, 2004]. Results from a multicenter phase II trial showed that median time to progression (TTP) for weekly paclitaxel in metastatic breast cancer patients was 4.7 months [Perez PA, 2001]. The median TTP for patients who had received no prior chemotherapy for metastatic disease, one prior regimen, and two prior regimens were 5.7 months, 4.6 months, and 2.7 months, respectively. Similarly, metastatic breast cancer patients treated with weekly paclitaxel (60-90 mg/m^2/1 hour iv infusion weekly) until disease progression or prohibitive toxicity had a median TTP of 4.86 months (range, 1.4-12.4) [Gori S, 2002]. Finally, a group of 74 Japanese ABC patients (48.7% were pre-treated with one line of chemotherapy) received paclitaxel by 1 h intravenous infusion at a dose of 80 mg/m^2 every week. Administration was continued for 3 weeks followed by a 1 week rest. The median time to progression was 4.8 months [Sato K, 2003]. The **VEX regimen** was recently investigated within a phase II trial currently ongoing in Istituto Europeo di Oncologia (IEO) (IEO number IEOS582/111; EudraCT Number: 2010-024266-21; title: “A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients”). Patients received vinorelbine 40 mg orally on days 1, 3 and 5 every week, cyclophosphamide 50 mg daily and capecitabine 500 mg 3 times a day. Among the 88 patients evaluable for efficacy, 42 were not pre-treated and 46 were pre-treated for metastatic disease. Median age was 54.4 years, 39% of patients had liver involvement.

	Median time to progression was 26.5 months and 9.6 months for untreated and pre-treated patients respectively. The proportion of patients free of progression at one year was 73% in the not pre-treated and 38% in the pre-treated group. As of January 2016, 24 patients were still on treatment. A total of 88 patients (42 untreated and 46 pre-treated) were analyzed for safety. One serious adverse event (ischemic heart attack) was reported. In the not pre-treated and pre-treated groups, grade 1-2 toxicities included nausea (50% and 17%), leucopenia (43% and 30%) increased liver enzymes (36% and 41%), hand and foot syndrome (26% and 11%). Grade 3 toxicities (hand and foot syndrome, hematologic and liver toxicities) were reported in 17% and 13% not pre-treated and pre-treated patients, respectively. No patient experienced grade 4 toxicities. The trial is still ongoing with a target accrual of 100 patients. Given the promising activity of the VEX regimen in a pre-treated population of advanced breast cancer patients and the good tolerability, the aim of the present trial is to investigate whether the VEX schedule may improve efficacy and tolerability as compared to standard paclitaxel treatment in advanced or metastatic ER-positive/HER-2 negative breast cancer patients. The concept of the VEX metronomic treatment is to administer the combination for as long as the patient has the possibility of deriving a benefit from it. The time to treatment failure (TTF) has been chosen as primary endpoint for this trial. TTF is defined as time from the date of randomization to the date when the final dose of trial treatment is administered. Chemotherapy may need to be stopped due to lack of tolerability, lack of efficacy or patient preference through subjective symptom assessment. TTF is a composite endpoint combining all these feasibility aspects of a treatment. It is therefore uniquely suited to the research question of the current trial. The secondary endpoints progression-free survival, disease control and safety will allow further assessment of the feasibility of the VEX metronomic treatment versus the paclitaxel monotherapy regimen. References: Eniu A, Palmieri FM, Perez EA. Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. Oncologist 2005; 10: 665-685. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666-2676. Miles DW, Chan A, Dirix LY et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010; 28: 3239-3247. Seidman AD, Berry D, Cirrincione C et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to

	trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008; 26: 1642-1649. Sparano JA, Wang M, Martino S et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008; 358: 1663-1671. Ando M, Watanabe T, Nagata K et al. Efficacy of docetaxel 60 mg/m2 in patients with metastatic breast cancer according to the status of anthracycline resistance. J Clin Oncol 2001; 19: 336-342. Tabernero J, Climent MA, Lluch A et al. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 2004; 15: 1358-1365. Perez EA, Vogel CL, Irwin DH et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001; 19: 4216-4223. Gori S, Mosconi AM, Basurtol C et al. Weekly paclitaxel in metastatic breast cancer patients: a phase II study. Tumori 2002; 88: 470-473. Sato K, Inoue K, Saito T et al. Multicenter phase II trial of weekly paclitaxel for advanced or metastatic breast cancer: the Saitama Breast Cancer Clinical Study Group (SBCCSG-01). Jpn J Clin Oncol 2003; 33: 371-376.
Primary Objective	To determine time to treatment failure (TTF) defined as the time from the date of randomization to the date when the final dose of trial treatment was administered.
Secondary Objectives	• Progression free survival (PFS) based on local Investigator assessment by RECIST 1.1. • Tolerability: adverse events according to CTCAE v4 • Disease control: best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only) lasting for at least 24 weeks, measured from randomization until first documentation of progressive disease • Overall survival (OS)
Number of patients	Randomization of 160 patients during approximately 24 months, with an additional 12 months of follow up after randomization of the last patient.
Inclusion criteria	• Histologically or cytologically confirmed HER2-negative locally advanced or metastatic (stage IV) breast cancer. • Maximum one prior line of chemotherapy for advanced or metastatic breast cancer. • Measurable or non-measurable, but radiologically evaluable (except for skin lesions), disease according to RECIST 1.1 criteria. • Female aged 18 years or older. • Life expectancy > 3 months. • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. • ER-positive disease by local laboratory, determined on most recent available tissue (latest biopsy of metastatic lesion, otherwise prior biopsy or surgical specimen). • If previously treated with a taxane in the neoadjuvant or adjuvant setting, the period from end of treatment to disease recurrence must have been > 12 months (> 365 days).

	• Radiation therapy, if given and regardless of site, must be completed at least 2 weeks prior to randomization. • Normal hematologic status, - Absolute neutrophil count ≥1000/mm^3 (1.0×10^9/L) - Platelets ≥ 100×10^9/L - Hemoglobin ≥ 9 g/dL (≥ 90 g/L)). • Normal renal function: serum creatinine ≤ 1.5 ULN or calculated creatinine clearance ≥ 50mL/min according to the Cockcroft-Gault formula. • Normal liver function: - Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total bilirubin (< 3 × ULN) is allowed - AST and ALT ≤ 3 × ULN; if the patient has liver metastases, ALT and AST must be ≤ 5 × ULN. • Women of child bearing potential must have documented negative pregnancy test within 2 weeks prior to randomization and agree to acceptable (non-hormonal) birth control during and up to 6 months after trial therapy. • Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to starting screening procedures and randomization. • The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.
Exclusion criteria	• More than one prior line of chemotherapy for advanced or metastatic breast cancer. • Previous treatment for advanced or metastatic disease with taxanes, or capecitabine or vinorelbine or oral cyclophosphamide. • More than 2 lines of previous endocrine therapy for locally advanced or metastatic breast cancer. • Known active central nervous system metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with history of CNS metastases or spinal cord compression are eligible if they are clinically and radiologically stable for at least 4 weeks before first dose of trial treatment and have not required high-dose steroid treatment in the last 4 weeks). • Peripheral neuropathy grade 2 or higher (CTCAE version 4.0). • Significant uncontrolled cardiac disease (i.e., unstable angina, myocardial infarction within prior 6 months), patients classified as having a New York Heart Association (NYHA) class III or IV congestive heart failure. • Pregnant or lactating. • Prior history of non-breast malignancy (except for adequately controlled basal cell carcinoma of the skin,

	carcinoma in situ of the cervix, in situ carcinoma of the bladder). • Any concurrent condition which in the Investigator's opinion makes it inappropriate for the patient to participate in the trial or which would jeopardize compliance with the protocol. • Contraindications or known hypersensitivity to the trial medication or excipients. • The use of any anti-cancer investigational agents within 30 days prior to expected start of trial treatment.
Assessments	Efficacy: • Tumor assessments according to RECIST v1.1. every 12 weeks (±2 weeks) until first documented progression. • Evaluation of tumor response and progression will be the task of the Investigator. Scans will not be centrally reviewed. • Follow-up will cease approximately 12 months after randomization of the last patient. Safety: • Laboratory evaluations should be done according to local standard of care. • Worst grade of adverse events will be recorded at beginning of next cycle. • All Serious Adverse Events must be notified to IBCSG within 24h of Investigator awareness.
Statistical considerations	Assuming the median TTF of paclitaxel is 4.5 months in this population and the median TTF of the VEX regimen is 7.5 months, with accrual averages of 3 per month for the first 6 months, 6 per month for the next 6 months, and 9 per month steady state for the next 12 months, we will complete recruitment of 160 patients within 24 months total accrual period, and we anticipate the required 123 TTF events to be available 6 months later. The final analysis will thus be based on data collected during 36 months from enrollment of the first patient, and results will be available within 42 months after enrollment of the first patient. The trial will have 80% power to detect the aforementioned difference in TTF using a two-sided, 0.05 significance level for the log-rank test. There will be one interim efficacy analysis performed to test for futility when 74 TTF events have been observed. Randomized patients who received at least one dose of the trial treatment will be included in the TTF analysis. For each arm separately, TTF distributions will be summarized using the method of Kaplan-Meier and the two-sided 95% confidence interval (CI) for the median TTF will be provided. TTF will be compared between groups by a stratified log-rank test using stratification factors defined for randomization. The toxicities and feasibility of each of the treatment arms will be assessed. PFS, OS, disease control rate and other measures of disease response will be evaluated for each treatment arm separately.

2. Trial schedule

(See section 13 for detailed examinations schedule)

	Screening period 28 days (35 days for imaging)	At randomi-zation	Day 1 of every cycle (4 weeks)	≤30 days after treatment stop	Every 12 (± 2) weeks from random. until first PD	- 1st progression - Death - Status 12 months after last pt randomized
Informed consent	(may be ob-tained prior to 28 days scree-ning period)					
Eligibility	X	*Record on 54-A Form*				
Clinical history	X	*Record on 54-A Form*				
Cardiac eva-luation: ECG	X					
Physical exam and vital signs	X		X *)	X		
Hematology: NC, TC, Hb	X		X	X		
Biochemistry: creatinine, bilirubin, AST, ALT ***)	X		X	X		
Pregnancy test	X					
Trial treatment			*Record on 54-Tx A or B Form*			
Adverse events		*Record baseline symptoms on 54-AE Form*	*Record worst grade on 54-AE Form*	*Record worst grade on 54-AE Form*		
Tumor measurements for RECIST 1.1	X				*During trial treatment **), record response on 54-TR Form*	
1st progression						*Record on 54-PD Form, if not recorded on 54-TR Form*
Survival or death						*Record survival on 54-E or death on 54-Death Form*

X = examination/assessment to be done

*) Arm B, VEX treatment: in Cycle 1, repeat hematology on Day 15
**) Report as long as the patient is on:
Arm A: paclitaxel
Arm B: *all three* drugs of the VEX treatment
***) ALT not mandatory on Day 1 of every cycle

3. List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CI	Confidence interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
DMC	Data Management Center
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EoT	End of Treatment
ER	Estrogen receptor
ERB	Ethical Review Board
FSTRF	Frontier Science and Technology Research Foundation
GCP	Good clinical practice
HER2	human epidermal growth factor receptor 2
HR	Hazard Ratio
IBCSG	International Breast Cancer Study Group
IC	Informed consent
ICH	International Conference on Harmonization
iDF	iDataFax
IRB	Institutional Review Board
MBC	Metastatic breast cancer
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not Evaluable
NYHA	New York Heart Association
OHRP	Office for Human Research Protection
ORR	Overall response rate
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression free survival
PI	Principal Investigator
PIS/IC	Patient information sheet / informed consent
PR	Partial response
PS	Performance status
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal
VEX	vinorelbine, cyclophosphamide, capecitabine

4. Background and scientific rationale

4.1. Breast cancer

Breast cancer (BC) is the most common form of malignant tumor in women worldwide, and incidence rates are as high as 99.4 per 100,000 women (World Health Organization 2011). Prognosis for patients with locally advanced or metastatic disease (ABC) remains poor, with a median survival of 2–4 years. About 10% of newly diagnosed BC patients present with ABC, and 30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease. Although many cytotoxic agents are active in breast cancer, advanced disease remains incurable and new treatment strategies are urgently needed. A large number of targeted anticancer agents are currently emerging, and some of these could be applicable to the treatment of advanced breast cancer. At the same time, breast cancer subtypes are being defined in far greater detail by molecular profiling [1]. As breast cancer is a heterogeneous disease, biological characteristics should be taken into account when deciding the most appropriate treatment strategy.

Luminal HER2-negative BC represents 60–65% of all newly diagnosed patients. Although prognosis in this subtype is generally good, still many women will relapse and luminal HER2-negative BC remains the most common subtype among metastatic breast cancer (MBC) patients [2].

Because of the chemosensitivity of this disease, the large majority of patients are, or eventually become, candidates for chemotherapy, either upfront or after failure of hormone therapy in endocrine-sensitive disease.

In this disease setting, where palliation is the primary goal of treatment and life expectancy is limited, toxicity and quality of life become important factors when deciding on therapeutic agents and schedules. In particular, in an attempt to improve the tolerability of prolonged chemotherapy administration, while maintaining and possibly improving treatment efficacy, alternative chemotherapy schedules and modalities, even with lower dosages, could be explored in this disease setting.

4.2. Treatment of advanced breast cancer

Classic cytotoxic chemotherapy still plays a major role in the management of MBC. A change in the paradigm of MBC chemotherapy has led, in the majority of patients, to replacement of aggressive, multidrug regimens by sequential single-agent therapies.

In the first-line treatment of HER2-negative ABC patients, various chemotherapy regimens can be used including taxanes, which are among the most active agents in BC. Single agent response rates range from 20% to 50% [3]. However, eventually all patients will progress with a median time to progression of 5 to 7 months. As an example of the single agent response rates, in the recent E2100 [4] and AVADO [5] randomized phase III trials in first-line HER2-negative ABC, the response rates were 22% and 46% and median progression free survival (PFS) was 5.8 and 8.1 months, respectively for the paclitaxel and docetaxel control arms. A weekly (qw) over a three-weekly (q3w) administration schedule of paclitaxel has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy [6, 7].

The median time to treatment failure (TTF) for docetaxel was investigated in patients previously treated with anthracyclines and ranged between 2.9 months and 5.2 months [8]. Weekly docetaxel showed 4.1 months of TTF in a subsequent trial [9]. In this trial, 52.4% of the patients were not pretreated, and the remaining were pretreated with at least one line of chemotherapy.

Results from a multicenter phase II trial showed that median time to progression (TTP) for weekly paclitaxel in metastatic breast cancer patients was 4.7 months [10]. Specifically, the median TTP for patients who had received no prior chemotherapy for metastatic disease, one prior regimen, and two prior regimens were 5.7 months, 4.6 months, and 2.7 months, respectively. Similarly, metastatic breast cancer patients treated with weekly paclitaxel (60-90 mg/m^2/1 hour iv infusion/weekly) until disease progression or prohibitive toxicity had a median TTP of 4.86 months (range, 1.4-12.4) [11]. Finally, a group of 74 Japanese ABC patients received paclitaxel by 1 h intravenous infusion at a dose of 80 mg/m^2 every week. Administration was continued for 3 weeks followed by a 1 week rest. The median time to progression was 4.8 months [12]. In this trial, 21.6% of the patients were not pretreated and 48.7% were pre-treated with only one line of chemotherapy.

4.3. Metronomic chemotherapy

Metronomic chemotherapy is a dosing-schedule strategy that includes a frequent, even daily, administration of chemotherapeutics at doses significantly below the maximum tolerated dose (MTD). No prolonged drug-free breaks are planned [13]. The metronomic approach significantly reduces toxicities and the need for growth-factor support to accelerate recovery from myelosuppression. Unlike dose-dense chemotherapy, which mainly targets proliferating tumor cells, the main targets of continuous metronomic chemotherapy are the endothelial cells of the growing vasculature of a tumor [14].

Another potential mechanism of action of agents included in a metronomic schedule is the DNA damage induced by continuous exposure. Therapies producing continuous DNA damage may significantly improve response rate and reduce the burden of chemotherapy related toxicity. Moreover the protracted exposure to low doses of chemotherapeutics has an antiangiogenic activity if compared with their cyclic administration at the maximum-tolerated dose [15].

The restoration of the anticancer effect of the immune system is among the new mechanisms identified for metronomic chemotherapy. There is growing evidence that anticancer immune responses can be crucial for the long-term control of cancer treated with chemotherapy [16]. In fact, some chemotherapeutic drugs (such as cyclophosphamide) may exert a beneficial effect by increasing antitumor immunity [17], and ultra-low noncytotoxic concentrations of selected antineoplastic agents might modulate the immune system [18].

4.3.1. Metronomic Cyclophosphamide and Capecitabine

The first trial using metronomic chemotherapy, conducted at the European Institute of Oncology, involved the administration of oral cyclophosphamide 50 mg daily and oral methotrexate 2.5 mg twice daily two days per week (CM regimen). Among 63 evaluable patients previously treated for metastatic breast cancer, this regimen yielded a response rate

of 19% and a clinical benefit (CB), defined as either objective response or stable disease longer than 24 weeks, of 32%, in the absence of serious toxicity, with a marked drop in circulating VEGF [19]. In a subsequent study at the same institution, 171 patients with ABC, either pre-treated or not with chemotherapy, were randomized to CM alone or CM + thalidomide. In this less heavily pretreated group of patients, CM alone yielded an objective response rate of 20.9% (95% CI 12.9-31.0%) and an overall CB of 41.5% (95% CI 34.0-49.3%) [20].

Capecitabine is an orally administered prodrug of fluorouracil and it is metabolically activated preferentially at the tumor site. Capecitabine shows antineoplastic activity and synergy with other cytotoxic agents including cyclophosphamide or docetaxel in animal models. Bioavailability after oral administration is close to 100%.

Its daily administration mimics the activity of a continuous intravenous infusion of fluorouracil, which has been shown to exert antiangiogenic activity in preclinical models. For its pharmacokinetic and toxicological features, capecitabine seems particularly suitable for metronomic administration.

Metronomic capecitabine has also proven antiangiogenic effects in tumor models of breast cancer [21].

In two small randomized trials, continuous use of low dose capecitabine (650 or 800 mg/m^2 b.i.d. with no drug-free breaks) proved to be just as effective in MBC patients as intermittent use of higher doses (1000 or 1250 mg/m^2 b.i.d. days 1–14 every 21 days) [22, 23].

Taguchi et al used a low dose schedule of capecitabine (852 mg/m^2 twice daily on days 1-21 of a 28-day cycle) as first-line therapy for 33 MBC patients. The authors reported a median progression free survival (PFS) of 6.9 months, with an overall survival (OS) of 24.8 months. Grade 3 toxicities included hand and foot syndrome (15%) and neutropenia (6%) [24].

The metronomic schedule of capecitabine was also evaluated in heavily pretreated patients with MBC. Sixty patients received oral capecitabine in a single daily dose of 1500 mg. The CB was 62% and the OS was 17 months. Grade 3–4 adverse events were uncommon [25].

Other studies evaluated the efficacy and safety of an all-oral doublet combination of cyclophosphamide and capecitabine. In the study of Wang et al, 68 anthracycline- and taxane-pretreated MBC patients received 21-day cycles of oral cyclophosphamide (65 mg/m^2 daily) and oral capecitabine (1,000 mg/m^2 twice daily on days 1–14 followed by a 7-day rest period). The median time to progression was 5.2 months and the OS was 16.9 months. The overall response rate (ORR) and CB were 30.3% and 53.0%, respectively. Treatment was well tolerated, and grade 3 hand–foot syndrome was reported by 4.4% of patients [26].

The same combination of metronomic chemotherapy with different dosages was evaluated in the study of Yoshimoto M et al. Fifty-one patients received capecitabine 828 mg/m^2 twice daily with cyclophosphamide 33 mg/m^2 twice daily, days 1–14 every 3 weeks. ORR was 44.4% and the CB was 57.8%. Hematologic toxicity included grade 3 leucopenia (26%) and neutropenia (16%). No grade 3 hand-foot syndrome was reported [27].

4.3.2. Oral Vinorelbine and the Metronomic Schedule

Vinorelbine (VRL), 5'nor-anhydrovinblastine, is a semi-synthetic vinca-alkaloid, which differs from other vinca-alkaloids by a modification of the catharanthine moiety [28, 29].

The mechanism of action of VRL is similar to that of other vinca-alkaloids, i.e., disruption of microtubules by their reversible binding to tubulin resulting in mitotic spindle dissolution and metaphase arrest in dividing cells. The inhibition of tubulin polymerisation with VRL is equal to or greater than with vindesine. The new oral formulation of vinorelbine (VRL) was introduced in clinical studies in 1994. The metronomic schedule of oral vinorelbine was tested in patients with metastatic cancer [30] at a dose of 50 mg three times a week as the tested metronomic schedule [31-33].

Oral vinorelbine at 70 mg/m^2, on days 1, 3, and 5, for 3 weeks on and 1 week off, every 4 weeks, was assessed in 34 elderly patients with metastatic breast cancer (median age 74 years) [34]. The ORR in 13 patients was 38%, and median PFS and overall survival were 7.7 months (95% CI 6.9–9.05 months) and 15.9 months (95% CI 13.1–15.91 months), respectively.

Escalating doses of oral metronomic vinorelbine (starting dose 30 mg every other day) and capecitabine (starting dose 800 mg/m^2 twice daily on days 1–14) were investigated in 36 patients. The recommended doses were 60 mg vinorelbine and 1,250 mg/m^2 capecitabine. [35]. The main toxicities were grade 2–3 neutropenia, anaemia, and nausea/vomiting, which were reported in fewer than 16.5% of patients.

4.4. The VEX regimen

The VEX regimen was recently investigated within a phase II trial currently ongoing in Istituto Europeo di Oncologia (IEO) (IEO number IEOS582/111; EudraCT Number: 2010-024266-21; title: "A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients"). Patients received vinorelbine 40 mg orally on days 1, 3 and 5 every week, cyclophosphamide 50 mg daily and capecitabine 500 mg 3 times a day.

Among the 88 patients evaluable for efficacy, 42 were not pre-treated and 46 were pre-treated for metastatic disease. Median age was 54.4 years, 39% of patients had liver involvement. Median time to progression was 26.5 months and 9.6 months for untreated and pre-treated patients respectively. The proportion of patients free of progression at one year was 73% in the not pre-treated and 38% in the pre-treated group. As of January 2016, 24 patients were still on treatment. A total of 88 patients (42 untreated and 46 pre-treated) were analyzed for safety. One serious adverse event (ischemic heart attack) was reported. The following table (presented at the IBCSG Annual Meeting on March 12, 2016) gives an overview of toxicities in 42 not pre-treated and 46 pre-treated patients:

	Untreated N=42				**Pretreated N=46**			
	G1	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Nausea	21	-	-	-	8	-	1	-
Diarrhea	19	-	-	-	14	-	-	-
Neutropenia	-	-	2	-	-	-	1	-

Leucopenia	2	16	-	-	8	6	1	-
Anemia	-	-	1	-	-	-		-
Hand-foot syndrome	5	6	2	-	-	5	2	-
increased AST/ALT	9	6	2	-	17	2	-	-
Alopecia	-	-	-	-	-	-	-	-
Astenia	-	-	-	-	14	-	-	-
Mucositis	-	-	-	-	-	-	1	-

No alopecia was observed. No patients experienced grade 4 toxicities. The trial is still ongoing with a target accrual of 100 patients.

4.5. Trial hypothesis

Based on the above mentioned efficacy data for the VEX regimen, we hypothesize that this regimen will be better tolerated and will result in longer time on treatment for women with ER-positive, HER2-negative, metastatic or locally advanced breast cancer, as compared to the standard paclitaxel monotherapy.

4.6. Overall risk-benefit assessment

The metastatic or advanced setting was chosen to evaluate this new therapy combination. The setting of incurable disease is acceptable to justify the evaluation of a potential new combination in breast cancer. Preliminary results from the pilot trial provide evidence of good tolerability and promising activity for the delivery of metronomic therapy with vinorelbine, cyclophosphamide and capecitabine in this patient population.

4.7. Rationale for the trial design

A 1:1 randomization will be performed to compare the metronomic VEX regimen with the conventional paclitaxel monotherapy. The presence of a randomized control arm will allow to assess the efficacy and tolerability of the metronomic regimen in a controlled fashion. The trial uses an open label design without blinding of treatments, as one treatment arm is administered orally, while the other is administered intravenously.

The concept of the VEX metronomic treatment is to administer the combination for as long as the patient has the possibility of deriving a benefit from it. The time to treatment failure (TTF) has been chosen as primary endpoint for this trial. TTF is defined as time from the date of randomization to the date when the final dose of trial treatment is administered. Chemotherapy may need to be stopped due to lack of tolerability, lack of efficacy or patient preference through subjective symptom assessment. TTF is a composite endpoint combining all these feasibility aspects of a treatment. It is therefore uniquely suited to the research question of the current trial. The secondary endpoints progression-free survival, disease control and safety will allow further assessment of the feasibility of the VEX metronomic treatment versus the paclitaxel monotherapy regimen.

5. Trial objectives and endpoints

5.1. Primary objective

The primary objective of the trial is to assess the combination of efficacy and tolerability, as measured by the time to treatment failure (TTF), of the first- or second-line combination treatment with vinorelbine, cyclophosphamide and capecitabine in comparison with paclitaxel monotherapy in estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2–), metastatic or locally advanced breast cancer patients, who need first- or second-line chemotherapy.

5.2. Primary endpoint

Time to treatment failure (TTF) is defined as the time from the date of randomization to the date when the final dose of trial treatment was administered.

5.3. Secondary objectives

To evaluate:

- Progression-free survival (PFS) based on local Investigator assessment by RECIST 1.1
- Safety and tolerability, as documented according to NCI CTCAE v4.0
- Disease control, based on RECIST 1.1 criteria
- Overall survival (OS)

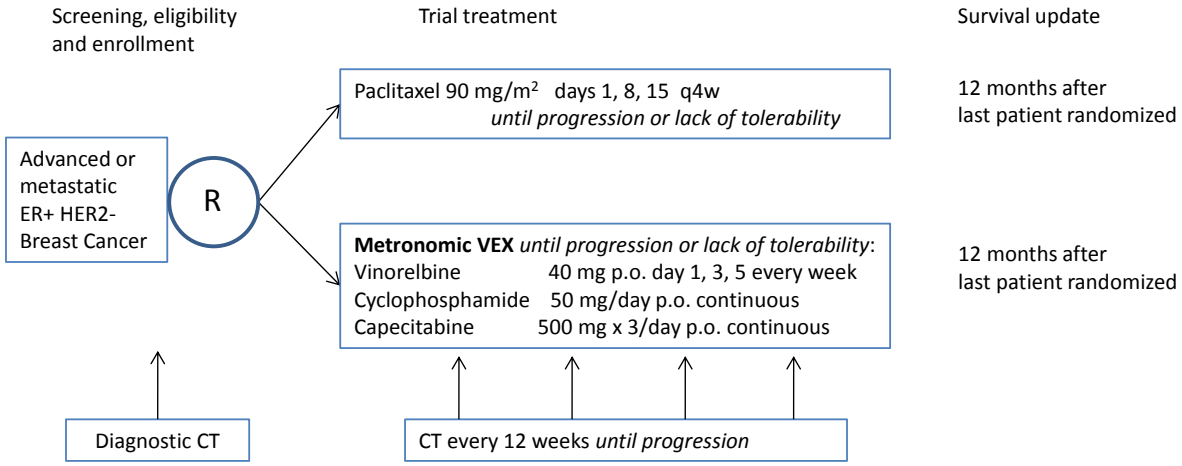
Secondary endpoints are defined in section 15.2.

6. Trial design, duration and termination

6.1. Trial design

This is a multi-center, randomized phase II trial that will randomize women with ER-positive, HER2-negative, advanced or metastatic breast cancer in a ratio of 1:1 to receive a metronomic regimen of vinorelbine, cyclophosphamide and capecitabine or the conventional paclitaxel monotherapy.

6.2. Trial schema



6.3. Sample size and trial duration

The trial will randomize a total of 160 patients.

Patients will be enrolled at approximately 20 sites in Italy.

The enrollment is expected to occur over a period of 24 months with accrual averages of 3 per month for the first 6 months, 6 per month for the next 6 months, and 9 per month steady state for the next 12 months. Individual patients' trial participation ends with the final documentation of survival status 12 months after the randomization of the last patient. Clinical visits are expected to span approximately 36 months after enrollment of the first patient. The final trial analysis is expected 42 months after the randomization of the first patient.

7. Patient selection

7.1. Inclusion criteria

7.1.1. Histologically or cytologically confirmed HER2-negative locally advanced or metastatic (stage IV) breast cancer.

7.1.2. Maximum of one prior line of chemotherapy for advanced or metastatic breast cancer.

7.1.3. Measurable or non-measurable, but radiologically evaluable (except for skin lesions), disease according to RECIST 1.1 criteria.

7.1.4. Female aged 18 years or older.

7.1.5. Life expectancy > 3 months.

7.1.6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (see Table 1 below).

7.1.7. ER-positive disease by local laboratory, determined on most recent available tissue (latest biopsy of metastatic lesion, otherwise prior biopsy or surgical specimen).

7.1.8. If previously treated with a taxane in the neoadjuvant or adjuvant setting, the period from end of treatment to disease recurrence must have been > 12 months (> 365 days).

7.1.9. Radiation therapy, if given and regardless of site, must be completed at least 2 weeks prior to randomization.

7.1.10. Normal hematologic status:

- Absolute neutrophil count $\geq 1000/mm^3$ ($1.0 \times 10^9/L$)
- Platelets $\geq 100 \times 10^9/L$
- Hemoglobin ≥ 9 g/dL (≥ 90 g/L)).

7.1.11. Normal renal function: serum creatinine $\leq$ 1.5 ULN or calculated creatinine clearance $\geq$ 50mL/min according to the Cockcroft-Gault formula.

7.1.12. Normal liver function:

- Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total bilirubin (< 3 × ULN) is allowed
- AST and ALT ≤ 3 × ULN; if the patient has liver metastases, ALT and AST must be ≤ 5 × ULN.

7.1.13. Women of child bearing potential must have a documented negative pregnancy test within 2 weeks prior to randomization and agree to acceptable birth control (non-hormonal, see section 10.2) during and up to 6 months after trial therapy.

7.1.14. Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to starting screening procedures and randomization.

7.1.15. The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.

7.2. Exclusion criteria

7.2.1. More than one prior line of chemotherapy for advanced or metastatic breast cancer.

7.2.2. Previous treatment for advanced or metastatic disease with taxanes, or capecitabine or vinorelbine or oral cyclophosphamide.

7.2.3. More than 2 lines of previous endocrine therapy for locally advanced or metastatic breast cancer.

7.2.4. Known active central nervous system metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with history of CNS metastases or spinal cord compression are eligible if they are clinically and radiologically stable for at least 4 weeks before first dose of trial treatment and have not required high-dose steroid treatment in the last 4 weeks).

7.2.5. Peripheral neuropathy grade 2 or higher (CTCAE version 4.0).

7.2.6. Significant uncontrolled cardiac disease (i.e., unstable angina, myocardial infarction within prior 6 months), patients classified as having a New York Heart Association (NYHA) class III or IV congestive heart failure (see Table 2 below).

7.2.7. Pregnant or lactating.

7.2.8. Prior history of non-breast malignancy (except for adequately controlled basal cell carcinoma of the skin, carcinoma in situ of the cervix, in situ carcinoma of the bladder).

7.2.9. Any concurrent condition which in the Investigator's opinion makes it inappropriate for the patient to participate in the trial or which would jeopardize compliance with the protocol.

7.2.10. Contraindications or known hypersensitivity to the trial medication or excipients.

7.2.11. The use of any anti-cancer investigational agents within 30 days prior to expected start of trial treatment.

Table 1. ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction.
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Table 2. NYHA functional classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

8. Randomization and stratification

This trial will use a web-based randomization system. Specific details for randomization are in the "IBCSG Registration/Randomization Procedures Manual" which is available on the IBCSG website (www.ibcsg.org).

8.1. Patient randomization procedure

8.1.1. Patient must sign informed consent to trial participation prior to screening procedures.

8.1.2. Screening procedures need to be done within 28 days before randomization (35 days for imaging) in order to verify eligibility (see section 7).

8.1.3. Access the IBCSG Registration/Randomization System (Step 1: Randomization) and provide the requested information as indicated on the Confirmation of Registration (54-A) Form. The date the Informed Consent Form was signed by the patient and the date signed by the Investigator are both required to complete randomization.

The Randomization System will provide the following information via email:

- Patient ID (randomization number)
- Treatment assignment

- Date of randomization

8.1.4. Submit the Confirmation of Registration (54-A) electronic case report form (eCRF) via iDataFax. The patient binder of eCRFs will be available in iDataFax within 24 hours of successful randomization.

8.2. Randomization Help Desk

The IBCSG Data Management Center (located at Frontier Science and Technology Research Foundation (FSTRF)) is responsible for developing and maintaining the IBCSG Registration/Randomization System. The Help Desk includes technical personnel and administrators of the registration programs at the Data Management Center in Amherst, NY, USA.

The Help Desk is available round the clock 7 days per week, except for New Year's Eve, Memorial Day, Independence Day, Thanksgiving Day, Christmas Day.

FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple Rd, Amherst, NY 14226 USA
Phone: +1 716 834 0900 Extension 7301
Fax: +1 716 832-8437
Email: bc.helpdesk@fstrf.org

8.3. Stratification

For randomization, patients will be stratified by

- Prior treatment for locally advanced or metastatic disease (no prior endocrine therapy or chemotherapy; prior endocrine therapy only; prior chemotherapy ± prior endocrine therapy)
- ECOG performance status 0 vs 1

Dynamic institution balancing will be done in order to balance randomized assignments within institutions.

8.4. Randomized Treatment Assignment

Patients will be randomized in a ratio of 1:1 to receive

- Arm A: conventional paclitaxel monotherapy
- Arm B: metronomic regimen of vinorelbine, cyclophosphamide and capecitabine

9. Treatment

Paclitaxel, vinorelbine, cyclophosphamide and capecitabine will be administered in this trial.

All drugs are commercially available and are used in clinical practice to treat advanced breast cancer. They will be locally sourced. No drugs will be supplied by the Sponsor. Labelling should be done following the local procedures and guidelines, if applicable.

Storage and handling will be according to local pharmacy standards; please consult also the respective SPCs at https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/

9.1. Trial treatments

Trial treatment should start within one week after randomization. Trial treatments will be administered in 4-week (28-day) cycles until progression, lack of tolerability, or until further trial treatment is declined (see section 9.5).

Treatment administration should comply with the protocol; compliance will be monitored by the Monitoring Team and/or Data Management Center. Details of dispensation and dosing are recorded on the eCRF. Patients on the experimental arm (Arm B) will be handed a patient diary on which they should be reminded to record all doses taken during one cycle. The patient should return the completed diary at the next visit.

9.2. Treatment Administration

Paclitaxel will be administered according to standard local practice.

Arm A Paclitaxel 90 mg/m^2 i.v. days 1, 8, 15 every 4 weeks, according to standard local practice

Treatment with the combination vinorelbine, cyclophosphamide and capecitabine is referred to as "VEX treatment" and will be administered as follows

Arm B Cyclophosphamide 50 mg orally once daily around 9am
Capecitabine 500 mg, orally 3 times a day (total 1500 mg/day) within 30 minutes after meals (breakfast, lunch, dinner)
Vinorelbine 40 mg orally days 1, 3, 5 each week (Monday, Wednesday, Friday) after lunch

9.3. Dose modifications and delays for paclitaxel

Refer to standard of care guidance or current clinical practice or currently approved Italian SPC for patients receiving paclitaxel, see also

https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/

For re-dosing with weekly paclitaxel, courses of paclitaxel should not be repeated until the neutrophil count is at least 1000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3 and in the absence of active infection. Patients who experience CTCAE Grade 4 thrombocytopenia (platelets <25,000/mm^3) or CTCAE Grade 3 peripheral neuropathy lasting < 7 days during paclitaxel therapy, should have dosage reduced by 20% for the subsequent course.

In the event that elevated liver function tests (LFT) (greater than three times the baseline values of AST/ ALT or greater than twice the baseline values ALP) are determined on a day that the patient is scheduled to receive treatment, paclitaxel therapy will be held and the values repeated weekly. If LFT elevation is persistent > 21 days and not due to progressive disease, the patient should permanently discontinue paclitaxel.

If values decrease within 14 days to grade ≤1, the patient may be retreated at the same paclitaxel dose. If within 1 week the patient again has an increase in LFTs (greater than three times the baseline values of AST/ ALT or greater than twice the baseline values of ALP), paclitaxel therapy will be held and the values assessed weekly. The patient may subsequently continue on therapy at a paclitaxel dose reduced to 80% at the Investigator's discretion. Doses

should not be reduced to less than 80% of 90 mg/m^2, otherwise treatment should be stopped permanently.

Paclitaxel dosing can be delayed by a maximum of 3 weeks (maximum 5 weeks from last dose of previous cycle).

9.4. Dose modifications and delays for VEX

Refer to standard of care guidance or current clinical practice or currently approved Italian Summary of Product Characteristics (SPC) for patients receiving vinorelbine, cyclophosphamide and capecitabine (VEX) treatment, see also https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/

9.4.1. Hematological toxicity

Complete blood count must be repeated every 4 weeks during the treatment.

Vinorelbine (V), cyclophosphamide (E) and capecitabine (X) will be administered at full dose if neutrophils are equal to or greater than 1500/mm^3 and platelets are equal to or greater than 100.000/mm^3. If granulocytes and/or platelets are lower than these values, treatment will be administered according to the following criteria:

	Neutrophils		
	Grade 0 or 1: >1.5 × 10^9/L	Grade 2: 1.0 – 1.5 × 10^9/L	Grade ≥3 <1.0 × 10^9/L
Platelets	Percentage of dose to be administered		
≥100 × 10^9/L	Continue V, E and X at 100% dose	Continue X at 67%**, and V and E at 50%* dose	Hold until resolved to Grade ≤1, then continue X at 67%**, and V and E at 50%* dose
Grade 1: 75 - 99 × 10^9/L	Continue X at 67%**, and V and E at 50%* dose	Hold until resolved to Grade ≤1, then continue with 100% dose	Hold until resolved to Grade ≤1, then continue X at 67%**, and V and E at 50%* dose
Grade ≥2: <75 × 10^9/L	Hold until resolved to Grade ≤1, then continue X at 67%**, and V and E at 50%* dose	Hold until resolved to Grade ≤1, then continue X at 67%**, and V and E at 50%* dose	Hold until resolved to Grade ≤1, then continue X at 67%**, and V and E at 50%* dose

* To achieve a 50% reduction of vinorelbine (V), patients will take 1 capsule of 20 mg 3 times a week

* To achieve a 50% dose reduction of cyclophosphamide (E), patients will take a tablet every other day;

** To achieve a 33% dose reduction of capecitabine (X), patients will take 1 tablet twice daily

If the hematological toxicity resolves to a grade of 1 or less, the dose may be escalated to the previous level at the Investigator's discretion.

Any platelets toxicity of grade ≥2 and granulocytes toxicity of grade ≥3 should be managed with temporary interruption of all chemotherapeutic agents until recovery at least to a grade 1, when treatment may be resumed with a 50% dose reduction. Re-escalation of drug doses should only be attempted if close monitoring is possible.

9.4.2. Non-hematological toxicity

Renal dysfunction: Cyclophosphamide, vinorelbine and capecitabine should be administered only in presence of normal renal function or grade 1 renal toxicity (serum creatinine < 1.5 upper normal limits and/or creatinine clearance ≥50 mL/min/1.73 m^2).

Cystitis: All patients should be instructed as to the importance of maintaining high fluid intake during cyclophosphamide therapy. If grade ≤2 cystitis occurs despite hydration, cyclophosphamide treatment should be stopped until recovery, and therapy with acetylcysteine, 1 tablet of 600 mg daily, should be administered until recovery, with the addition of antibiotic therapy in presence of fever. In case of repeated episodes of grade 2 cystitis, cyclophosphamide should be restarted, after resolution to at least grade 1, at 50% of dose. In case of grade ≥3 cystitis, cyclophosphamide should be permanently stopped.

Hepatic toxicity: If grade >2 hepatic toxicity occurs, vinorelbine (V), cyclophosphamide (E), and capecitabine (X) should be withheld until recovery to at least grade 1, and treatment with ademetionine may be administered.

Gastrointestinal toxicity: In case of grade ≥2 vomiting, stomatitis, or diarrhea, vinorelbine (V), cyclophosphamide (E), and capecitabine (X) should be stopped. Treatment may be resumed after recovery at least to grade 1 toxicity, starting with 50% dosage for E and V and 67% for X, with subsequent re-escalation to full dosage if tolerated.

Hand-foot syndrome: In case of grade 1 hand-foot syndrome, hydrating topic therapy should be started and capecitabine will be continued. In case of no benefit, as well as in case of grade 2 toxicity, the dose of capecitabine will be reduced to 67% (1 tablet twice daily) until recovery to at least grade 1. In case of grade 3 toxicity, capecitabine will be temporarily interrupted and resumed at 67% dose only after recovery to at least grade 1 toxicity, with subsequent re-escalation if tolerated.

Other toxicity: If deemed necessary, dosage may be reduced for other toxicities.

VEX treatment can be delayed by a maximum of 3 weeks (21 days) from the date of the last dose; in case of a longer delay, trial treatment has to stop (refer to note in section 9.5).

9.5. End of trial treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance.

The treatment of the individual patient will be discontinued in case of:

- Disease progression according to RECIST 1.1. as defined in section 12.
- Unacceptable adverse event(s).

- Delay of trial treatment by more than 3 weeks.
- Intercurrent illness that prevents further administration of trial treatment.
- Patient demonstrates an inability or unwillingness to comply with the treatment regimen and/or trial requirements.
- General or specific changes in the patient's condition which render her unacceptable for further trial treatment in the opinion of the treating Investigator.
- Patient withdraws consent to continue trial treatment.

Note: In Arm B (VEX), trial treatment is considered stopped as soon as one of the three drugs is stopped permanently. However, treatment with one or two of the VEX medications may be continued.

For patients who discontinue treatment for any reason other than objective disease progression, the date of first progression needs to be documented on the 54-PD Form. If the patient has not progressed yet, the date of the last visit will be reported on the 54-E Form, 12 months after the last patient was randomized.

After the trial treatment is stopped, future therapeutic decisions are at the discretion of the Investigator, with no restrictions. Patients showing RECIST 1.1 - defined PD can continue with trial treatment at the discretion of the Investigator as long as that is considered to be in the best interest of the patient and no new anticancer treatment is initiated.

The **End of Treatment (EoT)** is defined as the date of

- Arm A: the last dose of paclitaxel
- Arm B: the date when at least one of the three VEX drugs was administered for the last time

An end of treatment visit will be conducted within 30 days after EoT to report on any adverse events during this period (safety data).

In the absence of tumor progression, the patient will continue to be followed for SAE reporting according to a section 11.5 and for documented disease progression or a maximum of 12 months after randomization of the last patient, see section 13.5.

9.6. Removal from the trial

After a patient has been randomized, she becomes part of the clinical trial population and cannot be removed from the trial for any reason. If the patient decides to withdraw consent and declines any further participation with the trial requirements and/or declines further collection of data (see Section 16.5), the data recorded up to the time point of withdrawal will continue to be evaluated in the trial. If the patient discontinues treatment for any of the reasons listed in the prior subsection other than disease progression, she should continue to be followed according to the protocol (see Section 9.5) and eCRFs should be completed as described in Section 14.1.

Patients who have been randomized but never received any trial treatment for whatever reason (refusal, medical condition etc.) will have to be documented with a treatment form 54-TX A or 54-TX B (see section 13.4) stating this fact, but will not be followed further.

10. Safety

10.1. Adverse event profiles

The safety and adverse event profiles of the four drugs which constitute the trial treatment are well known. For details please refer to

https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/

10.2. Contraception, pregnancy, lactation

Trial treatment may have adverse effects on a fetus in utero. Non-pregnant, non-breast-feeding women of childbearing potential may be enrolled if they are willing to use effective contraception, defined as: intrauterine devices (without hormones), bilateral tubal occlusion, vasectomized partner or total abstinence. Oral, injectable, or implant hormonal contraceptives should not be used. Patients should start using or continue birth control from the start of trial treatment throughout the trial treatment.

Patients should be informed that taking the trial medication may involve unknown risks to the fetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above) for the duration of the trial treatment and 6 months thereafter. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

If a patient inadvertently becomes pregnant while on trial treatment, the event will be reported immediately, see Section 11.5. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to IBCSG without delay and within 24 hours of awareness if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to IBCSG.

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

11. Adverse event and serious adverse event reporting

11.1. Adverse event reporting

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE Version 4.0. The CTCAE is available for downloading on the internet at http://evs.nci.nih.gov/ftp1/CTCAE/About.html. A quick reference can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of trial medication until 28 days after all treatment discontinuation, regardless of whether it is considered related to a medication.

Any grade of any observed adverse event should be reported on the Adverse Event Form (54-AE) in iDataFax. Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

11.1.1. Severity / intensity

The adverse event severity grade provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the Investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g., severe nausea, mild seizure), and does not reflect the relationship to trial drug.

Severity grade for other adverse events not covered in the toxicity grading scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Note:

- Report the highest grade observed until resolution of the adverse event.
- Baseline symptoms and highest grade of adverse events will be recorded on the Form 54-AE.
- AEs should not be reported in a narrative description, but rather by using the applicable CTCAE v4.0 term.

11.1.2. Causality

The Investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not Suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

11.1.3. Action taken

The Investigator will report the action taken with trial drug(s) as a result of an AE or SAE, as applicable (e.g., discontinuation of trial drug(s)) and in case of a SAE Report if concomitant and/or additional treatments were given for the event.

11.2. Targeted adverse events

The presence or absence of the following AEs must be reported for every cycle on the Adverse Event Form (Form 54-AE). In addition, any other medically important AE should also be reported on Form 54-AE.

The AEs are listed by System Organ Class and Preferred Term:

11.2.1. Blood and lymphatic system disorders

- Neutropenia
- Thrombocytopenia
- Anemia

11.2.2. Skin and subcutaneous disorders

- Alopecia
- Palmar-plantar erythrodysesthesia syndrome

11.2.3. Immune system disorders

- Allergic reaction
- Anaphylaxis
- Aspartate aminotransferase increased

11.2.4. Metabolism and nutrition disorders

- Anorexia

11.2.5. Gastrointestinal disorders

- Diarrhea
- Vomiting
- Nausea
- Mucositis
- Constipation

11.2.6. Nervous system disorders

- Peripheral sensory neuropathy
- Optic nerve disorder (scotomata)

11.2.7. Infections and infestations

- Infection, specify

11.2.8. Musculoskeletal and connective tissue disorders

- Arthralgia or myalgia

11.2.9. General disorders and administration site conditions

- Injection site reactions
- Fatigue

11.2.10. Cardiac disorders

- Heart failure
- Acute coronary syndrome
- Sinus bradycardia
- Ventricular arrhythmia
- Supraventricular tachycardia

11.3. Otherwise reportable events

Certain types of events, as identified below, are reportable to IBCSG under the reporting processes and requirements for SAEs, even if there is no associated adverse event. These are considered "otherwise reportable events" and generally reflect circumstances that could lead to an increased risk of an adverse event. Like a SAE, an otherwise reportable event is to be reported to IBCSG within 24 hours of awareness and followed up to determine outcome, including the later occurrence of an associated SAE.

11.3.1. Pregnancy and lactation

Pregnancy will be reported within 24h of awareness on the Serious Adverse Event Form (54-SAE-A) in all cases.

Exposure during lactation will be reported within 24h on the 54–SAE-A Form.

In the event of pregnancy or lactation, all trial treatment must be discontinued.

Follow-up of the pregnancy is mandatory until the outcome has been determined. Outcome will be reported on the 54–SAE-B Form.

11.3.2. Relevant overdose of trial treatment

An overdose (accidental or intentional) of one of the trial treatment drugs is an event suspected by the Investigator or spontaneously notified by the patient.

The overdose has to be reported within 24h on the 54–SAE–A Form.

11.4. Serious adverse event (SAE)

11.4.1. Definition

A SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs from signature of informed consent until 28 days after stopping all trial treatment that, at any dose, results in any of the following:

- fatal (any cause except progression of disease)
- life-threatening
- requires or prolongs inpatient hospitalization
- persistent or significant disability/incapacity
- secondary (non-breast) malignancy
- congenital anomaly or birth defect (including neonatal deaths)
- constitutes an important medical event
- pregnancy or lactation

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

After completion of trial treatments, report all SAEs beyond 28 days that are considered at least possibly related to previous trial treatment. Cases of second (non-breast) malignancies and congenital abnormalities are to be regarded as SAEs, regardless of whether they occur during or after trial treatment. These events should be reported during the whole trial duration on the Serious Adverse Event eCRFs (54–SAE–A and 54–SAE–B).

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event that is serious, related to any of the trial treatment drugs and not listed as a known toxicity of the drug in the respective Italian SPC. All suspected unexpected serious adverse reactions judged by either the Investigator or IBCSG as the sponsor will be reported in accordance with applicable local regulations. IBCSG will report any SUSAR to EudraVigilance.

11.4.2. Exceptions to the definition

Hospitalizations occurring under the following circumstances are not considered to be serious adverse events:

- elective surgery
- those that occur on an outpatient basis and do not result in admission (hospitalization <24h)
- those that are part of the normal treatment or monitoring of the studied treatment
- progression of disease (by convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the Investigator considers that their clinical significance deserves reporting). Progression of disease is to be reported on Form 54-TR or Form 54-E and not as an SAE.

11.4.3. Causality assessment

The Investigator needs to assess the relationship between trial treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the trial treatment	Description
Suspected	The possibility that the trial treatment caused the event is deemed definite or probable or possible
Not suspected	The possibility that the trial treatment caused the event is deemed unlikely or unrelated

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the trial treatment will be considered and investigated.

The decision will be recorded on the SAE Form and if necessary the reason for the decision will also be recorded.

11.4.4. Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the trial. The expectedness assessment will be performed against the SPC of the respective trial treatment drugs.

11.5. Reporting SAEs

Any SAE or other reportable event (section 11.3) occurring in a patient after providing informed consent must be reported, including death due to any cause other than progression of breast cancer, which occurs within 28 days following cessation of treatment or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to one of the trial treatment drugs. Information about all such events will be collected and recorded on the IBCSG Serious Adverse Event eCRFs (54–SAE–A and 54–SAE–B).

To ensure patient safety, the IBCSG must be informed of each SAE using the procedures described below:

- The Investigator/MD responsible for the patient must complete a Serious Adverse Event (SAE-A) eCRF in English within 24 hours of awareness via iDataFax. A copy is automatically forwarded to the IBCSG Safety Office for medical review.
- Queries may be issued by the IBCSG Safety Office; a timely response by the Investigator to all SAE-related queries is crucial.
- Follow-up information should be completed via iDataFax on the Serious Adverse Event (SAE-B) eCRF as soon as available but within 15 days of the initial report, even if the event reported in the SAE-A eCRF is not yet resolved. If the event is not resolved within 15 days, revise the original Serious Adverse Event (SAE-B) eCRF in iDataFax to report the final resolution.
- All SAEs that have not resolved upon discontinuation of the patient's participation in the trial must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

- If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided within 24 hours.
- Photocopies of all examinations carried out with the dates on which they were performed should be sent by fax or DFSend into the DataFax system. Care should be taken to ensure that the patient's identity is protected and the Patient ID number is properly included on ALL pages of any reports. For laboratory results, include the laboratory normal ranges. Please also note on each page that the information is "SAE related" so it can be properly categorized in iDF.
- In the event the eCRF system is not working, the SAE Forms can be found in the trial site file or downloaded from the IBCSG trial webpage and sent via fax or DFSend into the DataFax system within 24 hours of awareness.

If an SAE (SAE-A and SAE-B Forms) was submitted by fax or DFSend, the original forms and the fax confirmation sheet(s) must be kept at the Participating Center.

The IBCSG will inform Pierre Fabre Pharmacovigilance and other appropriate persons about all SAEs within 48 hours of receipt at the IBCSG.

The IBCSG will record the SAE and prepare a monthly SAE report. Principal Investigators will receive the summary report on a monthly basis, and these reports can be found on the IBCSG web site (www.ibcsg.org).

12. Disease assessment, response and progression (RECIST 1.1)

12.1. Introduction

All enrolled patients will be assessed for disease response and progression according to the revised Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [36]. In this trial, patients may have measurable or non-measurable disease (see definitions below). Patients will be re-evaluated every 12 weeks until documented progression.

Response and progression-free survival will be assessed using RECIST 1.1 criteria. Please consult the "RECIST 1.1 Training Workbook" available on www.ibcsg.org .

12.2. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during treatment and follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan should generally be performed using a $\leq$ 5 mm contiguous reconstruction algorithm. MRI is acceptable for certain situations (e.g., body scans).

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules) and $\geq$10 mm. In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

Ultrasound is not useful in assessment of lesion size and is not accepted as a method of assessment.

FDG-PET is not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a PET/CT scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT scan performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT scan (with i.v. and oral contrast), then the CT scan portion of the PET/CT can be used for RECIST measurements.

12.3. Measurability of tumor at baseline

12.3.1. Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20 mm by chest X-ray.

  Reminder: A lesion in a previously irradiated area is not eligible for measurable disease.
- **Malignant lymph nodes**: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan, assuming the slice thickness is ≤ 5 mm. At baseline and in follow-up, only the short axis will be measured.

12.3.2. Non-measurable disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured.

Non-measurable lesions/sites of disease and special considerations:

- Small non-nodal lesions (longest diameter < 10 mm in CT scan).
- Small lymph nodes (short axis ≥ 10 and < 15 mm). Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.
- Bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Leptomeningeal disease
- Ascites

- Pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions.
- Tumor lesions situated in a previously irradiated area, or subjected to other locoregional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion.
- Abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques.

12.4. Selection of target lesions

Target lesions should be identified, measured and recorded. At baseline, there can be up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and recorded as the baseline sum of diameters. Lymph nodes selected as target lesions should always have the short axis recorded. All other lesions should always have their longest diameters recorded. The sum of diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

12.5. Selection of non-target lesions

Non-target lesions should be identified. All other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

For non-target lesions, measurements are not required, but the presence or absence of each should be noted throughout follow-up.

12.6. Evaluation of target lesions (measurable disease)

All target lesions will be measured at each tumor assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all target lesions. Lymph nodes selected as target lesions must each have reduction in the short axis to <10 mm in order for the response to be considered complete. In this case, the sum of diameters may be >0.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions (see section 12.8) denotes disease progression.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on trial.

Note: All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a target lesion is thought likely to have disappeared, use "0 mm."

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

12.7. Evaluation of non-target lesions

All non-target lesions will be assessed at each tumor assessment, and compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (< 10 mm).
- Non-CR/non-PD: Persistence of one or more non-target lesions (non-CR).
- Progression (PD): unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease, or an overall substantial increase in tumor burden that merits treatment discontinuation.

When no imaging is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesions are evaluated at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

12.8. Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique or findings thought to represent something other than tumor). If a new lesion is equivocal, (e.g., because of its small size) the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scan documents that there is definitely a new lesion, then progression should be declared using the date of the previous scan when the lesion was discovered.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g., brain metastases) are considered new lesions.

Note: The "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

12.9. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.10. Determination of time point response

Based on the responses of target lesions, non-target lesions, and the presence or absence of new lesions, the overall response will be determined at each tumor evaluation time point, according to Table 3 or Table 4 below.

12.10.1. For patients with measurable disease

Table 3. Measurable Disease - Overall Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR / non-PD*	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.			

12.10.2. For patients with non-measurable disease only

Table 4. Non-Measurable Disease - Overall Response

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD*	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.		

12.11. Determination of best overall response

Best overall response is defined as best response recorded from randomization across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial.

12.12. Progression-free Survival

The date of progression is the date that objective progression was first documented. Progression-free survival (PFS) is defined as time from randomization until documented disease progression according to RECIST 1.1 criteria or death, whichever occurs first. For patients without progression, follow-up will be censored at the date of the survival update 12 months after the randomization of the last patient, unless death occurs within a short period of time (12 weeks, corresponding to the interval of tumor re-evaluation) following the date last known progression-free, in which case the death will be counted as a PFS event.

Patients who discontinue treatment prior to documented disease progression (see Section 9.5), including those who initiate non-protocol therapy prior to progression, will be followed for disease progression, for a maximum of 12 months after the randomization of the last patient. A new (non-breast) cancer malignancy has to be reported on the 54-SAE Forms; such patients must continue to be followed for progression of the original breast cancer.

13. Clinical and laboratory evaluations and follow-up

13.1. Screening

The following examinations should be done within a maximum of 28 days before randomization. The clock for the screening period starts when the first procedure is performed. If examinations were done prior to 28 days before randomization, they have to be repeated. The diagnostic imaging must be done within 35 days before randomization.

13.1.1. Obtain informed consent for screening evaluations and trial participation (informed consent may be obtained earlier than within 28 days before randomization.).

13.1.2. Medical history including ER status, HER2 status, prior endocrine treatment and chemotherapy in the locally advanced or metastatic setting.

13.1.3. Clinical and radiological (by CT scan or MRI) tumor assessments of chest/abdomen/pelvis, within 35 days before randomization.

13.1.4. Bone scan and FDG-PET if medically indicated.

13.1.5. Cardiac evaluation: Electrocardiogram (ECG).

13.1.6. Physical examination according to local standards including vital signs, ECOG Performance Status, height, weight.

13.1.7. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

13.1.8. Biochemistry:

Liver function tests: total bilirubin, ALT, AST;

Kidney function test: creatinine.

13.1.9. For patient of childbearing potential: pregnancy test within 2 weeks prior to randomization.

13.1.10. Baseline symptoms and adverse events graded according to CTCAE v4.0 (record on baseline adverse events form, 54-AE). Baseline symptoms and adverse events should be recorded from signature of informed consent to prior to start of treatment.

13.2. Day 1 of every treatment cycle

The following evaluations have to be done on Day 1 of every treatment cycle (or within 3 days before these dates):

13.2.1. Physical examination according to local standards including vital signs, ECOG Performance Status and weight.

13.2.2. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

Arm B, VEX treatment: in cycle 1, repeat hematology on Day 15

13.2.3. Biochemistry:

Liver function tests: total bilirubin, AST;

Kidney function test: creatinine.

13.2.4. Collection of any adverse event observed in the previous cycle and assignment of appropriate adverse events grade according to the NCI CTCAE Version 4.0.

13.2.5. Arm B, VEX treatment: Compliance assessment (check patient diary, file in patient records as source data; hand out new patient diary for next cycle).

13.3. Tumor assessments

Tumor measurements according to RECIST 1.1 criteria (see section 12) have to be done at baseline, and every 12 weeks (± 2 weeks) from randomization until first disease progression.

13.3.1. Clinical and radiological (by CT scan or MRI) tumor assessments.

13.3.2. Bone scan and FDG-PET will be done if clinically indicated at the same time points.

13.4. After end of trial treatment

Within 30 days after end of trial treatment (or at the time of decision to stop the trial treatment if the decision is taken >30 days after last dose):

13.4.1. Physical examination according to local standards including vital signs, ECOG Performance Status and weight.

13.4.2. Hematology: Hemoglobin, platelet count, white blood cell count including differential (absolute neutrophil count).

13.4.3. Biochemistry:

Liver function tests: total bilirubin, AST;

Kidney function test: creatinine.

13.4.4. Collection of any adverse event and assignment of appropriate adverse events grade according to the NCI CTCAE Version 4.0.

13.4.5. Arm B, VEX treatment: Compliance assessment (check patient diary).

13.5. Follow-up prior to documented disease progression

In case trial treatment was stopped prior to documented disease progression, the information below should be documented for patients until first progression, or for a maximum of 12 months after randomization of the last patient. Visits should take place every 12 weeks (± 2 weeks).

13.5.1. Tumor evaluation according to RECIST 1.1 for determination of disease progression. Report disease progression on the 54-PD Form.

13.5.2. Serious adverse events up to 28 days after stop of all trial treatment:

- Arm A: stop of paclitaxel
- Arm B: stop of *all three* VEX drugs.

13.6. Survival follow-up

If a patient dies, this is to be recorded on the 54-Death Form at the time of death.

12 months after the randomization of the last patient into the trial, survival status needs to be documented for all alive patients on the 54-E Form.

14. Data submission

We will conduct the trial according to the ICH Good Clinical Practice (GCP) guidelines. Keeping accurate and consistent records is essential to a cooperative trial. The following forms are to be submitted at the indicated times by the participating institutions for each patient:

14.1. Case report forms schedule

Forms	*Description/Name*	*Forms Submission* *ALL data should be completed in iDataFax (iDF) (unless otherwise specified)*
Informed Consent Form	Consent to participation in clinical trial	Obtain before randomization and prior to screening procedure and keep with patient records as documentation (hard copy only).
Registration and Randomization		
54-A	Confirmation of Registration Form	Complete in iDF after you have randomized the patient in the IBCSG Registration/ Randomization System. Patient will be available in iDF **within 24 hours** of successful registration.
Baseline		
54-AE	Adverse Events Form	To record any symptoms present at randomization and prior to start of trial treatment, complete in iDF within 1 week of randomization.
During trial treatment		
54-TX-A	Protocol Therapy Form, Arm A	Complete in iDF at the end of each cycle until treatment stops.
54-TX-B	Protocol Therapy Form, Arm B	Complete in iDF at the end of each cycle until treatment stops. Note for Arm B: Stopping **of at least one trial medication** denotes stopping VEX treatment.
54-AE	Adverse Events Form	Complete in iDF at the end of each treatment cycle to report highest grade for all events during this cycle
54-TR	Tumor Response Form	Complete in iDF every 12 weeks up to end of trial treatment.
Event-driven forms to be submitted after end of treatment (EoT)		
54-AE	Adverse Events Form	Complete one month after stop of trial treatment, to report highest grade for all events observed up to 30 days after treatment stops.
54-PD	First Progression Form	Complete in iDF at first progression
54-Death	Death form	Complete in iDF at time of death
54-E	Survival Follow-up Form	Complete in iDF 12 months after randomization of the last patient for survival and disease status.
Event-driven forms		
54-SAE-A	Serious Adverse Event Form A - Initial report	Complete in iDF within 24 hours of the SAE awareness. If iDF is not available, fax the form within 24 hours to DataFax.
54-SAE-B	Serious Adverse Event Form B - Follow-up report	Complete in iDF as soon as follow-up available, at the latest within 15 days of the initial report (54-SAE-A). If event is not resolved in 15 days, update 54-SAE-B again at the time of resolution.
54-COC	Change of Consent Form	Complete in iDF if there is any change in patient's consent to participate in the trial, see Section 16.5.2.

The iDF User Manual and the Data Managers' Manual for this trial contain instructions for completing and submitting forms using the iDataFax system.

14.2. Signing and submitting forms

An Authorization Log (see section 14.5) should be completed at each Participating Center to identify the persons who are authorized to complete CRFs.

CRFs should be completed on-line in iDataFax. Reports (lab, etc.) and any other non-CRF data will need to be sent to the DataFax system via fax or DFSend. Full instructions on submitting forms are available on the IBCSG website (www.ibcsg.org). Also available on the website is a list of fax numbers that are available for faxing CRFs.

14.3. Data management

Data collected in this trial will be submitted to the IBCSG Data Management Center in Amherst, NY, USA. The Data Management Center will process the data and will generate queries and forms requests. The Data Quality Control Office will oversee overall data submission and query resolution. The IBCSG Coordinating Center in Bern, Switzerland will provide medical review and summary of SAEs. The IBCSG Statistical Center in Boston, MA, USA will perform the data analysis.

14.4. Investigator Site File

Each Participating Center should keep documentation about this trial in an Investigator Site File (ISF). Please arrange the documentation in the order foreseen in the ISF index which will be provided by IBCSG. The following documents should be included (list is not complete):

- Protocol and appendices
- Activation letter
- Accrual reports
- Amendments
- Copy of signed Protocol Signature Pages
- Sample CRFs including blank SAE Forms
- Patient Diary template
- Data Managers' Manual
- Obvious Corrections Document and Signature Page
- Randomization Manual
- iDataFax (iDF) Manual
- Patient information and Informed Consent templates approved by Ethics Committee
- Ethics Committee and Health Authority approval of protocol, hospital management approval (=Delibera), Patient Information Sheet and Informed Consent, amendments
- Ethics Committee review of SAE, Investigators' alert, and other documents
- Correspondence with Ethics Committee and Health Authority (if applicable)
- Certificate of clinical trial insurance
- Agreement with IBCSG
- Center activation email(s) from IBCSG Data Management Center (protocol and amendments, if any)
- Correspondence with / Information issued by IBCSG Coordinating Center, Data Management Center

- SAE Reports sent from IBCSG Data Management Center
- Normal laboratory values/reference ranges
- Laboratory Certifications
- CV of Principal Investigator and Co-Investigators, GCP certificates
- Trial Training Certificates issued by IBCSG Center Training Office
- Documentation of any training done internally (e.g., by use of IBCSG Training Confirmation Log)
- Authorization Log
- Center Information Sheet
- Patient identification log (see section 14.6)
- Weblink to ICH GCP guidelines/Declaration of Helsinki and updates
- Audit certificates / monitoring follow-up letters

14.5. Authorization log

The Principal Investigator (PI) should identify the other members of the Clinical Trial Team who are supervised by the PI, appropriately qualified and approved to provide information in CRFs, queries, etc. Instructions for completing the Authorization Log can be found in the Authorization Log Manual, posted on the IBCSG website. All changes need to be communicated to IBCSG by updating and emailing the Authorization Log.

14.6. Patient identification log

No patients' names should be used in CRFs or any other documentation transmitted to IBCSG central offices. The only item used to identify a patient is the Patient ID (Randomization Number). It is therefore imperative that the local data manager keep an identification log for all patients entered in this trial including:

- Patient's name
- Patient ID issued by the IBCSG Registration/Randomization System
- Date of birth
- Date of randomization

15. Statistical considerations

The primary objective of the trial is to assess the combination of efficacy and tolerability, as measured by the time to treatment failure (TTF), of the combination treatment by vinorelbine, cyclophosphamide and capecitabine in comparison with paclitaxel monotherapy in estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2–), metastatic or locally advanced breast cancer patients, who need first- or second-line chemotherapy. A total of 160 patients will be stratified (Section 8.3) and randomized in a 1:1 allocation (80: 80 patients) to the experimental and control groups.

15.1. Primary Objective

15.1.1. Primary endpoint

The primary efficacy endpoint of TTF (defined in Section 5.2) will be compared between treatment groups, using an intention-to-treat analysis approach.

15.1.2. Design and Sample Size Determination

160 patients will be stratified and randomized using 1:1 allocation of 80 patients to treatment with VEX and 80 patients to treatment with paclitaxel. Enrollment is expected to proceed with an accrual rate of 3 patients per month over the first 6 months, 6 patients per month over the next 6 months, and 9 patients per month over the subsequent 12 months, and the final analysis after an additional 12 months of follow-up. The final analysis will thus be based on data collected during 36 months from enrollment of the first patient, and results will be available within 42 months after enrollment of the first patient (allowing 6 months for data cleaning and statistical analysis).

The sample size was determined in consideration of the primary objective. The median TTF of patients in this population treated with paclitaxel is assumed to be 4.5 months. When 123 TTF events are observed, there is 80% power to detect an improvement in median TTF from 4.5 with paclitaxel to 7.5 months with VEX (40% reduction in hazard, HR=0.60; two-sided α=0.05). If the above assumptions hold, we anticipate 123 TTF events to be observed between 30 and 36 months from enrollment of the first patient. Exponential failures and a 1% per month dropout rate were assumed for the sample size calculation, which was carried out using East 5.4 (Cytel Inc., Cambridge, MA, USA). One interim efficacy analysis to assess for futility is planned (see Section 15.4).

15.1.3. Analysis of Primary Endpoint

TTF will be compared between groups by a stratified log-rank test using stratification factors defined for randomization. The hazard ratio with two-sided 95% CI will be estimated using a stratified Cox proportional hazards model. The distribution of TTF will be summarized for each treatment group using the method of Kaplan-Meier; median TTF with two-sided 95% confidence interval (CI) will be summarized. TTF will also be summarized separately according to previous chemotherapy yes vs no.

15.2. Secondary objectives

15.2.1. Safety and tolerability

Adverse events (AE) will be collected using CTCAE v4.0. The maximum grade of each targeted AE while on treatment will be determined, and the frequencies summarized and tabulated according to grade and treatment assignment, with two-sided exact binomial 95% CIs, and compared between the two randomized arms.

15.2.2. Disease Control

Disease control is defined as best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only) lasting for at least 24 weeks, measured from

randomization until first documentation of progressive disease. Disease control will be summarized according to treatment assignment as proportion with two-sided exact binomial 95% CI, and compared between the two randomized arms. Disease control will also be summarized separately according to line of chemotherapy received.

15.2.3. Progression free survival (PFS)

PFS (defined in Section 12.12) will be compared between groups by a stratified log-rank test using stratification factors defined for randomization. The statistical power of this comparison at the final analysis is likely to be less than 80%. The hazard ratio with two-sided 95% CI will be estimated using a stratified Cox proportional hazards model. The distribution of PFS will be summarized for each treatment group using the method of Kaplan-Meier; median PFS with two-sided 95% confidence interval (CI) will be summarized. PFS will also be summarized separately according to line of chemotherapy received.

15.2.4. Overall survival (OS)

Overall survival is defined as the time from the date of randomization to death from any cause. For patients who are lost to follow-up or who have no documentation of death at the time of final analysis, follow-up will be censored at the date of last assessment of vital status. The distribution of OS will be summarized for each treatment group using the method of Kaplan-Meier; median OS with two-sided 95% CI will be calculated. OS will also be summarized separately according to line of chemotherapy received.

15.3. Definitions of Trial Populations

Efficacy analysis population: All randomized patients, who receive at least one dose of trial treatment.

Safety population: All patients receiving at least one dose of trial treatment will be included in assessments of safety and tolerability.

15.4. Interim Analyses

One interim analysis will be performed for futility when 74 TTF events have been observed. It is anticipated that this number of TTF events will be observed approximately 22 months after first patient is enrolled. Results will be presented to the Data and Safety Monitoring Committee (DSMC), which may recommend discontinuation of the trial if it is clear at that point that the alternative hypothesis of an improved TTF associated with VEX compared with paclitaxel is unlikely to be shown. A one-sided boundary based on the O'Brien-Fleming criteria will be used to guide the DSMC deliberations.

15.5. Accrual

The overall accrual goal of this trial is 160 patients. We anticipate that the accrual rate will be approximately 3 patients per month during the first 6 months and 6 patients per month during the next 6 months as Participating Centers activate the trial. A steady state of 9 patients per month is anticipated during the subsequent 12 months, for a total accrual duration of 24 months.

15.6. Data and Safety Monitoring

The trial will be presented for review to the IBCSG DSMC at each of their semi-annual meetings. Accrual, safety and accumulation of TTF events will be monitored. The interim futility analysis will also be presented after 74 TTF events have been observed.

16. Ethical aspects, regulatory approval, and patient informed consent

The Investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. The Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

16.1. Ethical Review Board/Ethics Committee

All protocols and the patient Informed Consent Forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The Ethics Review Board (ERB) / Institution Review Board (IRB) written, signed approval letter/form must contain approval of the designated Investigator, the protocol (identifying protocol title and version number), and of the patient Informed Consent. Documentation of Ethics Committee approval(s) must be sent to the IBCSG Data Management Center prior to enrollment of the first patient. The IBCSG Ethics Committee also approves the protocol and reviews it annually.

Any modifications made to the protocol will be reviewed by the IBCSG Ethics Committee and must also be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the Investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of IBCSG.

16.2. Regulatory approval procedures

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol-related documents including patient information and Informed Consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the IBCSG Data Management Center prior to Participating Center activation.

16.3. Protection of human patients

The IBCSG has an Office for Human Research Protection (OHRP) Federal Wide Assurance (FWA00009439) and follows all of the policies and procedures that are part of that assurance.

All potential patients for this trial will receive a full explanation of the trial, its purpose, treatments, risks, benefits, and all of the other items listed in section 16.4. Additional institution-specific sections should be added to Appendix I as needed.

The medical record must be available for review by the IBCSG monitors and audit team and regulatory authorities as described in section 17.6.

Serious Adverse Event (SAE) Reports are distributed monthly. In addition they are available on the IBCSG website (www.ibcsg.org) for participating Centers.

16.4. Informed Consent

Informed Consent for each patient will be obtained prior to initiating any trial procedures in accordance with the "IBCSG Patient Information Sheet and Informed Consent" (See Appendix I). One signed and dated copy of the Informed Consent must be given to each patient and the original copy must be retained in the Investigator's trial records. The Informed Consent Form must be available in the case of data audits. Verification of signed Informed Consent and the date signed are required for randomization to this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician (http://www.wma.net/en/30publications/10policies/b3/index.html). The potential patient should also be informed of her right to not participate or to withdraw from the trial at any time.

If the patient is in a dependent relationship to the physician or gives consent under duress, the Informed Consent should be obtained by an independent physician. By signing this protocol, the Investigator agrees to conduct the trial in accordance with the "Guideline for Good Clinical Practice" E6(R1) ICH Tripartite Guideline and the "Declaration of Helsinki."

The IBCSG recognizes that each institution has its own local, national, and international guidelines to follow with regard to Informed Consent. Therefore, we provide a template information sheet and Informed Consent Form (Appendix I), which can be downloaded and edited to incorporate information specific to your institution (see www.ibcsg.org). The template Patient Information Sheet and Informed Consent (PIS/IC) has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki". The final version should receive the Institutional Review Board/ Local Ethics Committee approval in advance of its use. Centers should send their locally modified PIS/IC to the IBCSG Data Management Center for review and approval before submitting to their Ethics Committee.

16.5. Premature withdrawal

16.5.1. Cessation of trial treatment

Patients have the right to refuse further trial treatment at any time during the trial. Patients may also be withdrawn from trial treatment at any time at the discretion of the Investigator due to an adverse event, or based on any other relevant medical condition. Such patients will remain in the trial and data collection will continue according to protocol.

16.5.2. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue to be evaluated in the trial.

Withdrawal of consent should be documented in both the medical records and in the eCRF (Form 54-COC). For the patient's safety, an end of treatment visit should be performed.

17. Governance and Administrative Considerations

17.1. Insurance

IBCSG will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local Center should report all alleged claims immediately to the IBCSG.

17.2. Governance

The Trial Committee consisting of the Chairman of the IBCSG Scientific Committee, the Trial Chair, the Trial Statistician, The Director of Statistics and Data Management and the IBCSG Director is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. The Trial Committee is also responsible for the translation of recommendations of the IBCSG Data and Safety Monitoring Committee into decisions.

General partition of responsibilities:

The Trial Committee has the authority to make and implement any final decisions, and may recommend the termination/early termination of the trial.

The IBCSG Foundation Council decides on the termination/early termination of the trial.

17.3. Data and Safety Monitoring Committee (DSMC)

The trial will be presented for review to the IBCSG Data and Safety Monitoring Committee (DSMC) at each of their semi-annual meetings. Accrual, safety and accumulation of TTF events will be monitored.

17.4. Publication of trial results

IBCSG will publish the results of the trial based on the final trial report.

17.5. Premature discontinuation of the trial

The trial may be discontinued early in parts or completely if the information on the trial treatment leads to doubt as to the benefit/risk ratio.

The trial can be terminated at any time if the authorization and approval to conduct the Study is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

17.6. Quality Assurance

The IBCSG conducts trials according to the "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997). The Trial IBCSG Data Manager reviews each CRF. In addition, the IBCSG Medical Reviewer reviews each case at specific timepoints. The IBCSG may conduct periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and may perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from IBCSG or its designees, or to health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the Center will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review trial progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits/phone calls will include but not be limited to review of the following aspects: patient Informed Consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, trial treatment administration, patient compliance with the regimens, concomitant therapy use and quality of data.

17.7. Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact IBCSG or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The Investigator should document and explain any deviations from the approved protocol and promptly report them to IBCSG and to the EC concerned in accordance with the applicable EC policies and procedures. If the Investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by IBCSG and approved by the IRB/IEC/REB it cannot be implemented. All protocol deviations will be documented.

17.8. Data protection

A unique Patient Identification (ID)/Randomization Number will be assigned by the IBCSG Registration/ Randomization System to each patient registered into the trial. The names of the patients will not be disclosed to IBCSG.

Only the Patient ID will be used to identify a patient on the eCRF. Identification of patients must be guaranteed at the Participating Center. In order to avoid identification errors, Centers should keep a Patient Identification Log containing the patients' name, year of birth, and the Patient ID allocated by IBCSG.

Regulatory authorities and the pertinent Ethics Committee (ERB/IRB) may have access to patient data on-site. IBCSG audit or monitoring personnel will also have access to such data on-site.

17.9. Record Retention

The Center must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient Informed Consent statement, laboratory printouts, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. IBCSG guarantees access and availability of the data entered into iDataFax for at least 15 years after the termination of the trial.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to IBCSG and the local Ethics Committee at least one month in advance.

18. Confidentiality

The protocol, CRFs and other protocol-related documents are confidential and are the property of IBCSG.

19. References

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International Breast Cancer Study Group Statistical Center

A randomized phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel as first-line or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer

MEtronomic TrEatment Option in advanced bReast cAncer: the METEORA-II trial (IBCSG 54-16)

Statistical Analysis Plan

Version	Author	Date	Status
1	Subrina Farah, MS	May 2020	Primary endpoint definition and analysis for interim analysis.
2	Meredith Regan, ScD	Nov 2021	Full SAP for primary analysis

1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Prognosis for patients with locally advanced or metastatic breast cancer (ABC) remains poor, with a median survival of 2–4 years. About 10% of newly-diagnosed breast cancer patients present with ABC, and 30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease.

In the first-line treatment of patients with HER2-negative ABC, various chemotherapy regimens can be used including taxanes, which are among the most active agents in breast cancer. Single-agent response rates range from 20 to 50%. However, eventually all patients' disease will progress with a median time to progression of 5 to 7 months.

The VEX regimen was recently investigated within a phase II trial in Istituto Europeo di Oncologia (IEO). Patients received vinorelbine 40 mg orally on days 1, 3 and 5 every week, cyclophosphamide 50 mg daily and capecitabine 500 mg 3 times a day. Among the 88 patients evaluable for efficacy, 42 were not pre-treated and 46 were pre-treated for metastatic disease. Median time to progression was 26.5 months and 9.6 months for untreated and pre-treated patients respectively. The proportion of patients free of progression at one year was 73% in the not pre-treated and 38% in the pre-treated group. As of January 2016, 24 patients were still on treatment. A total of 88 patients (42 untreated and 46 pre-treated) were analyzed for safety. One serious adverse event (ischemic heart attack) was reported. In the not pre-treated and pre-treated groups, grade 1-2 toxicities included nausea (50% and 17%), leucopenia (43% and 30%) increased liver enzymes (36% and 41%), hand and foot syndrome (26% and 11%). Grade 3 toxicities (hand and foot syndrome, hematologic and liver toxicities) were reported in 17% and 13% not pre-treated and pre-treated patients, respectively. No patient experienced grade 4 toxicities.

Given the promising activity of the VEX regimen in a pre-treated population of patients with ABC and the good tolerability, the aim of the METEORA-II trial is to investigate whether the VEX schedule may improve efficacy and tolerability as compared to standard paclitaxel treatment in patients with ER-positive/HER-2 negative ABC.

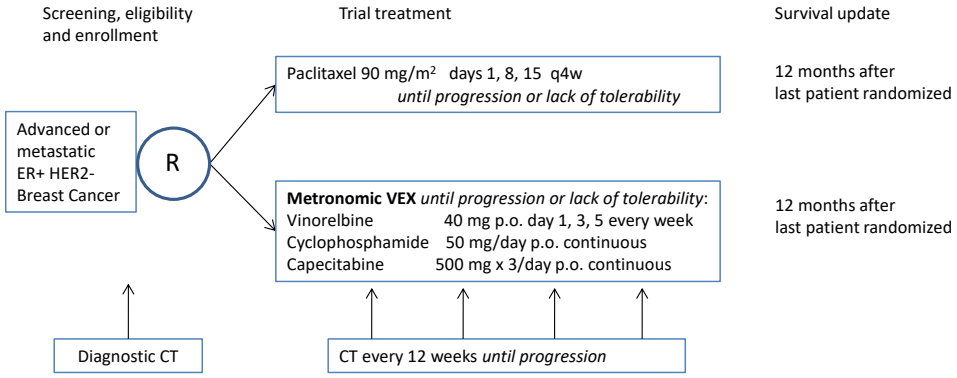
The concept of the VEX metronomic treatment is to administer the combination for as long as the patient has the possibility of deriving a benefit from it. The time to treatment failure (TTF) is chosen as primary endpoint for this trial, defined as time from the date of randomization to the date when the final dose of trial treatment is administered. Chemotherapy may need to be stopped due to lack of tolerability, lack of efficacy or patient preference through subjective symptom assessment. TTF is a composite endpoint combining all these feasibility aspects of a treatment. It is therefore uniquely suited to the research question of the current trial. The secondary endpoints progression-free survival, disease control and safety will allow further assessment of the feasibility of the VEX metronomic treatment versus the paclitaxel monotherapy regimen.

1.2 TRIAL DESIGN

IBCSG TRIAL 54-16 METEORA II

Project Title:	A randomized phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel as first-line or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer Study Chair: Elisabetta Munzone, MD (EIO, Milan)
Patient Population:	Patients with ER-positive/HER2-negative advanced or metastatic breast cancer (stage IV), measurable or non-measurable, but radiologically evaluable (except for skin lesions).
Patient Entry:	Maximum of one prior line of chemotherapy for advanced or metastatic breast cancer. If patients were previously treated with a taxane in the neoadjuvant or adjuvant setting, the period from end of treatment to disease recurrence must have been > 12 months.
Activation Date:	13 February 2017 (first patient randomized 13 September 2017)
Closure Date:	31 January 2021 (last patient entered 14 January 2021)
Final Accrual:	140 patients (Target 160 patients)

Schema



Patients were randomized in a 1:11 ratio, stratified by:

- Prior treatment for locally advanced or metastatic disease (no prior ET or CT, prior ET only, prior CT±ET)
- ECOG performance status (0 vs 1).

Treatment Schedules

- Arm A: Paclitaxel 90 mg/m^2 days 1, 8, 15 q4 weeks;
- Arm B: Cyclophosphamide 50 mg orally once daily, capecitabine 500 mg, orally 3 times a day (1500 mg/day), vinorelbine 40 mg orally days 1, 3, 5 each week.

Patients continue to receive assigned treatment until objective progressive disease (PD), symptomatic deterioration, unacceptable toxicity, death, or refusal to continue treatment, whichever occurs first.

1.2.1 Statistical Design

160 patients will be stratified and randomized using 1:1 allocation of 80 patients to treatment with VEX and 80 patients to treatment with paclitaxel. Enrollment is expected to proceed with an accrual rate of 3 patients per month over the first 6 months, 6 patients per month over the next 6 months, and 9 patients per month over the subsequent 12 months, and the final analysis after an additional 12 months of follow-up. The final analysis will thus be based on data collected during 36 months from enrollment of the first patient, and results will be available within 42 months after enrollment of the first patient (allowing 6 months for data cleaning and statistical analysis).

The sample size was determined in consideration of the primary objective. The median TTF of patients treated with paclitaxel is assumed to be 4.5 months. When 123 TTF events are observed, there is 80% power to detect an improvement in median TTF from 4.5 with paclitaxel to 7.5 months with VEX (40% reduction in hazard, HR=0.60; two-sided α=0.05). If the above assumptions hold, we anticipate 123 TTF events to be observed between 30 and 36 months from enrollment of the first patient. Exponential failures and a 1% per month dropout rate were assumed for the sample size calculation, which was carried out using East 5.4 (Cytel Inc., Cambridge, MA, USA). One interim efficacy analysis to assess for futility is planned.

One interim analysis will be performed for futility when 74 TTF events have been observed. It is anticipated that this number of TTF events will be observed approximately 22 months after first patient is enrolled. Results will be presented to the Data and Safety Monitoring Committee (DSMC), which may recommend discontinuation of the trial if it is clear at that point that the alternative hypothesis of an improved TTF associated with VEX compared with paclitaxel is unlikely to be shown. A one-sided boundary based on the O'Brien-Fleming criteria will be used to guide the DSMC deliberations.

1.2.2 Summary of interim analyses

The IBCSG DSMC regularly reviews the trial at its twice-yearly meetings. One interim efficacy analysis to assess for futility was planned when 74 TTF events had been observed. This was conducted at the meeting in July 2020 (based on 122 patients enrolled as of 31 March 2020 and data retrieval 27 May 2020; 75 TTF events had been observed). The DSMC recommended the trial continue as planned.

1.3 TRIAL CONDUCT

The submission of METEORA (activated August 2016) was rejected by the Italian regulatory agency (AIFA) because the protocol referred to the trial as a Phase III study, but the primary endpoint was time to treatment failure, which AIFA would not accept as a phase III primary endpoint. The trial was re-written as phase II trial, renamed as METEORA-II, and resubmitted to AIFA and IEO ethics committee. Activities for METEORA activation ceased. The METEORA-II study was activated on 13 February 2017.

The accrual goal was 160 patients for this trial, anticipated to be enrolled over 24 months with 12 months additional follow-up for primary analysis, which would have completed enrollment before

the end of 2019. With slow but steady enrollment, a revised completion date of 31 December 2020 was targeted. After discussions with the IBCSG DSMC at its December 2020 meeting, the IBCSG leadership decided to proceed with closure of enrollment on 31 January 2021, even though the enrollment goal had not been reached. The decision considered that the enrollment had been ongoing for more than 3 years and the enrollment rate had slowed, 1 to 2 patients per month over the past 6 months, suggesting approximately 12 more months to reach 160 patients enrolled. The other consideration was that enrollment of at least 138 patients would still allow the trial to report results with adequate statistical power. The statistical design targeted 123 primary endpoint events (time to treatment failure), defined based upon discontinuation of trial treatment, and could be reached based upon enrolled patients well prior to anticipated enrollment of 160 patients. Thus the enrollment closure would allow more timely reporting of the results without any compromise of trial integrity.

1.4 TRIAL REGISTRATION

The trial is registered in ClinicalTrials.gov: NCT02954055 and in the European Medicines Agency's (EMA) European Clinical Trials database: EudraCT 2016-002200-39.

2 EFFICACY ANALYSIS PLANS

2.1 OBJECTIVES

2.1.1 Primary objective

To assess efficacy, as measured by the time to treatment failure (TTF), of the first-line combination treatment with vinorelbine, cyclophosphamide and capecitabine (VEX) in comparison with paclitaxel monotherapy in ER+/HER2–, metastatic or locally advanced breast cancer patients, who have progressed under previous endocrine therapy.

2.1.2 Secondary objectives

To evaluate:

- Progression-free survival (PFS) based on local Investigator assessment by RECIST 1.1
- Safety and tolerability, as documented according to NCI CTCAE v4.0
- Disease control, based on RECIST 1.1 criteria
- Overall survival (OS)

2.2 ANALYSIS POPULATIONS

Efficacy analysis population: All randomized patients who receive at least one dose of trial treatment.

Safety population: All randomized patients who receive at least one dose of trial treatment.

(thus the two populations are the same)

2.3 ENDPOINT DEFINITIONS

2.3.1 Primary Endpoint

Time to treatment failure (TTF) is defined as the time from the date of randomization to the date when the final dose of trial treatment was administered. [sic; protocol §5.2]

In implementation: The above endpoint definition from protocol §5.2 but is **incorrect**, as it would bias in favor of Arm B (VEX) which includes 3 agents vs. Arm A (paclitaxel). The protocol had addressed this issue by clearly defining **End of Treatment (EoT)**, per protocol §9.5:

"The End of Treatment (EoT) is defined as the date of

- Arm A: the last dose of paclitaxel
- Arm B: the date when at least one of the three VEX drugs was administered for the last time"

but the correction erroneously was not followed through to the endpoint definition.

It is also stated in protocol §9.5: "After the trial treatment is stopped, future therapeutic decisions are at the discretion of the Investigator, with no restrictions. Patients showing RECIST 1.1 - defined PD can continue with trial treatment at the discretion of the Investigator as long as that is considered to be in the best interest of the patient and no new anticancer treatment is initiated." Which is in direct conflict with the primary endpoint for VEX.

Thus time to treatment failure (TTF) is defined as: the duration of time between the date of randomization to the end of treatment date (from protocol §9.5),

- Arm A: the last dose of [iv] paclitaxel; and to account for the time of active IV drug +7 days is added to the date of last dose.
- Arm B: the date when at least one of the three [oral] VEX drugs was administered for the last time. (the CRF records the date first medication permanently discontinued)

The eCRF also captures date decision to (A) stop trial treatment; or (B) discontinue at least one trial medication. This is not used for the endpoint; this was for determining that end-of-treatment visit occurred within appropriate time interval.

Cycles are 28 days. Regarding delays for toxicity that would result in discontinuation:

- Paclitaxel dosing can be delayed by a maximum of 3 weeks (maximum 5 weeks from last dose of previous cycle);
- VEX treatment can be delayed by a maximum of 3 weeks (21 days) from the date of the last dose; in case of a longer delay, trial treatment has to stop (refer to note in protocol §9.5). Note: In Arm B (VEX), trial treatment is considered stopped as soon as one of the three drugs is stopped permanently. However, treatment with one or two of the VEX medications may be continued.).

Indications of dose not taken, and the intervals between cycles were reviewed to ensure within the appropriate periods as specified above, as part of checking the permanent discontinuation dates. Those cycles that were not within the appropriate time interval were queried by the DMC to

confirm whether there was a delay exceeding protocol guidelines. Note specifically for VEX arm, because of pandemic the medications were sometimes provided for 2 cycles and an in-person visit skipped to minimize visits and these could appear as if delays between cycles; these were all queried to confirm that medications continued, and the database queries and correspondence documents this.

If delay was beyond protocol specification, then:

- End of treatment date was redefined (adjusted) based upon last dose prior to extended delay beyond protocol specification;
- The reason for end of treatment was redefined based upon reason for delay (mostly recorded on eCRF as reason off schedule);
- Subsequent cycles were marked as ones that should not have occurred and were not counted toward other variables describing treatment administration; the AEs will be reported both with and without those cycles (see subsequent sections).
- All such cases and cycles will be listed in the report.

2.3.2 Secondary Endpoints

Progression-free survival (PFS): [Protocol §12.12] The date of progression is the date that objective progression was first documented. Progression-free survival (PFS) is defined as time from randomization until documented disease progression according to RECIST 1.1 criteria or death, whichever occurs first. For patients without progression, follow-up will be censored at the date of the survival update 12 months after the randomization of the last patient[*], unless death occurs within a short period of time (12 weeks, corresponding to the interval of tumor re-evaluation) following the date last known progression-free, in which case the death will be counted as a PFS event.

Patients who discontinue treatment prior to documented disease progression (see [protocol] §9.5), including those who initiate non-protocol therapy prior to progression, will be followed for disease progression, for a maximum of 12 months after the randomization of the last patient*. [In case of] A new (non-breast) cancer malignancy … such patients must continue to be followed for progression of the original breast cancer.

*See note in next subsection regarding follow-up update, which was requested prior to 12 months after randomization of the last patient.

In implementation: the interval for death as event is 14 weeks for the first (week 12) scan, allowing that scan window is 12 ± 2 weeks; and thereafter it was 16 weeks as 6/8 patients died within 16 weeks of their last scan and the 2/8 that did not had much larger intervals of 30 and 60 weeks, providing a clear natural division (and determined without regard to treatment assignment).

Patients without imaging after randomization who did not die within 12 weeks from randomization had PFS censored at date of randomization (1 day).

Note for those who discontinued treatment prior to documented disease progression, it cannot be determined whether progression is prior to or after subsequent therapy (which could include protocol-assigned therapy received after EOT outside of the protocol). Whether disease progression was documented prior to or after TTF date will be determined.

A final note, TTF duration may be slightly greater than PFS duration, because PFS date is the date first suspicion of progression and sometimes additional tests or imaging were conducted to confirm progression, at which point treatment was permanently discontinued.

Disease Control is defined as best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only) lasting for at least 24 weeks, measured from randomization until first documentation of progressive disease. [Protocol §15.2.2] **Best overall response** is defined as best response recorded from randomization across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial. [Protocol §12.11]

In implementation: BOR is across all time points until reported EOT, as the post-treatment PD eCRF captured only PD date after EOT; and the follow-up (E) eCRF captured date last adequate disease assessment if patient still without PD. However because disease control is non-PD for ≥24 weeks, this endpoint can be updated using the subsequent post-treatment PD date and follow-up form.

Overall survival is defined as the time from the date of randomization to death from any cause. For patients who are lost to follow-up or who have no documentation of death at the time of final analysis, follow-up will be censored at the date of last assessment of vital status. [Protocol §15.2.4]

2.3.3 Relevant Study Procedures

Trial treatment should start within one week after randomization.

Patients who have been randomized but <u>never received any trial treatment</u> for whatever reason (refusal, medical condition etc.) will have to be documented with a treatment form, but will not be followed further.

Trial treatments will be administered in **4-week (28-day) cycles** until progression, lack of tolerability, or until further trial treatment is declined. The treatment of the individual patient will be **discontinued in case of**:

- Disease progression according to RECIST 1.1. as defined in section 12.
- Unacceptable adverse event(s).
- Delay of trial treatment by more than 3 weeks
- Intercurrent illness that prevents further administration of trial treatment.
- Patient demonstrates an inability or unwillingness to comply with the treatment regimen and/or trial requirements.
- General or specific changes in the patient's condition which render her unacceptable for further trial treatment in the opinion of the treating Investigator.

- Patient withdraws consent to continue trial treatment.

Note: In Arm B (VEX), trial treatment is considered stopped as soon as one of the three drugs is stopped permanently. However, treatment with one or two of the VEX medications may be continued (data were not collected after first medication was discontinued).

After the trial treatment is stopped, future therapeutic decisions are at the discretion of the Investigator, with no restrictions. Patients showing RECIST 1.1 - defined PD can continue with trial treatment at the discretion of the Investigator as long as that is considered to be in the best interest of the patient and no new anticancer treatment is initiated. (data were not collected)

- Paclitaxel dosing can be delayed by a maximum of 3 weeks (maximum 5 weeks from last dose of previous cycle).
- VEX treatment can be delayed by a maximum of 3 weeks (21 days) from the date of the last dose; in case of a longer delay, trial treatment has to stop (refer to note in [protocol] §9.5).

End of treatment visit: Within 30 days after end of trial treatment (or at the time of decision to stop the trial treatment if the decision is taken >30 days after last dose) to report on any AEs during this period.

Imaging: Tumor measurements according to RECIST 1.1 criteria have to be done at baseline, and every 12 weeks (± 2 weeks) from randomization until first disease progression. Tumor assessments include: clinical and radiological (by CT scan or MRI) tumor assessments and bone scan and FDG-PET will be done if clinically indicated at the same time points.

For patients who discontinue treatment for any reason other than objective disease progression, the date of first progression needs to be documented (54-PD Form). In the absence of tumor progression, the patient will continue to be followed for SAE reporting according and for documented disease progression or a maximum of 12 months after treatment stop [protocol §13.5] Visits should take place every 12 weeks (± 2 weeks). If the patient had not yet experienced disease progression, the date of the last adequate disease assessment (and PD, if applicable) will be reported on the 54-E Form, ~12 months after the last patient* was randomized.

***Survival follow-up**: 12 months after the randomization of the last patient, survival status needs to be documented for all alive patients on the 54-E Form.

In implementation: The request for 54-E forms was distributed in Q3'2021 which was less than 12 months after the last patient enrolled, in preparation for the Q4'2021 database lock. This form also asked for confirmation of, and allowed update of, the date objective progression first documented.

Adverse events: from the first dose of trial medication until 28 days after all treatment discontinuation, regardless of whether it is considered related to a medication. The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality classified according to the NCI CTCAE Version 4.0. The presence or absence of the following 25

AEs were systematically queried for every cycle; in addition, any other medically important AE should also be reported:

- Blood and lymphatic system disorders (neutropenia, thrombocytopenia, anemia),
- Skin and subcutaneous disorders (alopecia, palmar-plantar erythrodysesthesia syndrome)
- Immune system disorders (allergic reaction, anaphylaxis, aspartate aminotransferase increased)
- Metabolism and nutrition disorders (anorexia)
- Gastrointestinal disorders (diarrhea, vomiting, nausea, mucositis, constipation)
- Nervous system disorders (peripheral sensory neuropathy, optic nerve disorder (scotomata))
- Infections and infestations
- Musculoskeletal and connective tissue disorders (arthralgia or myalgia)
- General disorders and administration site conditions (injection site reactions, fatigue)
- Cardiac disorders (heart failure, acute coronary syndrome, sinus bradycardia, ventricular arrhythmia, supraventricular tachycardia)

Serious adverse events up to 28 days after stop of all trial treatment: Arm A: stop of paclitaxel, Arm B: stop of *all three* VEX drugs.

2.4 FOLLOW-UP

As described above, study participation ended with EOT visit for patients who discontinued treatment for objective disease progression. Patients who discontinued treatment for other reasons were to continue imaging for progression for up to 12 months. Updated survival follow-up was sought prior to database lock for patients who were last known alive when they had completed trial participation.

The median and IQR follow-up for survival will be calculated, overall and by treatment assignment. If a majority (at least 50%) of the patients have died, then it may be calculated as the median OS of surviving patients. Otherwise, the median follow-up will be estimated from the OS censoring distribution (i.e., by reversing the event/censoring indicator for OS).

2.5 TESTS AND ESTIMATES

The efficacy analysis approach is intention-to-treat (ITT) in the defined efficacy analysis population.

The primary objective will be investigated by comparing TTF distribution between two treatment groups using two-sided stratified logrank test (H0: TTF1=TTF2; Ha: TTF1≠TTF2), with $\alpha=0.05$. The test statistic and p-value will be taken from the stratified Cox PH model score test; Efron method for handling ties. Hazard ratios (VEX / paclitaxel, so that HR<1 indicates reduced hazard

of event with VEX and HR>1 indicates increased hazard of an event with VEX) will be estimated from a stratified Cox PH model, with two-sided Wald 95% CIs.

Kaplan-Meier estimates of the TTF distributions will be calculated for each of the treatment groups, with reporting of the median, 6- and 12-month TTF; the SEs will use Greenwood's formula and the pointwise 95% CIs will be obtained using complementary log-log transformation of the SDF.

We will check the proportional hazards assumption by visually assessing the plot of log(-log(survival)) versus log of survival time for parallelism. This will be done overall, and according to strata.

The protocol specified a subgroup analysis in which TTF was summarized separately according to previous chemotherapy yes vs no; estimates and CIs will be reported, with HRs and CIs estimated from a model with covariate-by-treatment interaction.

2.5.1 Stratification and Randomization

Randomization was stratified according to

- Prior treatment for locally advanced or metastatic disease (no prior endocrine therapy or chemotherapy; prior endocrine therapy only; prior chemotherapy ± prior endocrine therapy)
- ECOG performance status 0 vs 1.

Dynamic institution balancing was done in order to balance randomized assignments within institutions.

In implementation: We had concern about (3 x 2=) 6 strata with 140 patients. The distribution of prior treatment was roughly (25%, 60%, 15%) and of ECOG PS (80%, 20%). Thus stratification for modeling will be reduced to 4 categories:

- PS 1 regardless of prior treatment;
- PS 0 according to prior treatment {no prior ET/CT; prior ET only; prior CT±ET}

Sensitivity analysis for the primary endpoint will be performed, changing the strata to be each of the two factors individually and reported for the original combined factors (i.e., for full 6 strata).

2.6 ANALYSIS COMPONENTS

2.6.1 CONSORT

In order to complete the CONSORT flow diagram, the following will be tabulated, overall and according to treatment assignment:

- First and last dates patients enrolled, number of centers that enrolled patients (overall only)
- Number of patients randomized
- Number of patients who started (included in efficacy analysis population) vs never started (excluded from efficacy analysis population) treatment, with reasons never started; there

will also be a listing of these patients (patid, center code, rando date, treatment assignment, reason)

- Number of patients who discontinue treatment & number not discontinued at db lock
- Number in efficacy analysis population who WC/LFU; listing all such patients also (patid, center code, randomization date (mon/yy), treatment assignment, number cycles, reason treatment discontinuation, WC/LFU status and date)

2.6.2 Enrollment, Follow-up Compliance

Accrual figures/tables:

- Monthly accrual: bar chart of numbers of patients enrolled by month, from Sep'17 to Jan'21, with horizontal lines indicating expected monthly accrual;
- Cumulative accrual: bar chart of cumulative number of patients enrolled, from Sep'17 to Jan'21, with line for targeted cumulative enrollment;
- Tabulate accrual per center (with center code & name, sorted largest to smallest enrollment), by year (2017-2020*) and total (*include Jan'21 with 2020)
- Tabulate/list per center: N randomized, N started treatment, N discontinued treatment (TTF event) at db lock, N with alive at db lock, N alive with updated status at db lock

There was no review for deviations from inclusion/exclusion criteria for this trial.

The status of survival follow-up submission, according to center, will be summarized. Tables:

- Tabulation providing for each center: N randomized, N died, N alive, month/year of last vital status for those alive

2.6.3 Stratification

For both the randomized population, and the efficacy analysis population. Tables and listing:

- Distribution of stratification factors (individually and combined), overall and according to treatment assignment
- Distribution of stratification factors (individually and combined) according to center and according to year randomized
- Cross-tabulation of factors as reported at (and used for) randomization vs actual. The randomization form (RA form) collects the values entered into the IBCSG randomization system and used for stratification of the randomization assignment. If these values are incorrect then they are amended on the Registration form (54-A form). For primary and secondary overall analyses we will use the stratification factors entered on randomization form. For tabulating characteristics and subgroup analyses, the actual values entered in the A form will be reported (stratification factors also will be tabulated; and will be labeled as such).
- Listing of incorrect stratification factors (patid, center code, treatment assignment, randomization date (mon/yr), both stratification factors: RA and A forms).

2.6.4 Patient, Disease and Prior Treatment Characteristics

Characteristics are taken from the Registration (54-A) form; IBCSG standard is to use A form when available and otherwise resort to the RA (randomization) internal form. RA is as reported at time of randomization & never changes; A form would correct a value, if necessary. In this trial, the A-form data are complete, thus no need to combine info from both forms.

- Stratification factors: ECOG PS at randomization, prior treatment for ABC
- Patient characteristics: age at randomization, ECOG PS at randomization (A form), BMI at randomization (derived)
- Disease characteristics: weeks from MBC diagnosis to enrollment (derived); ER status determination (primary or metastatic tissue); measurable disease yes/no
- Prior treatment characteristics: Prior treatment for ABC (A form: none, ET only, CT±ET), prior ET±CDK4/6 inhibitor use (derived: no prior ET, ET without CDK46i, ET+CDK46i just prior to enrollment, ET+CDK46i previously)
- Baseline AEs

Tables/figures/listings, for the efficacy analysis population:

- Tabulation, N patients randomized, stratification factors, patient disease & treatment characteristics; overall and according to treatment assignment; age in groups needed for CT.gov & EudraCT should be included
- Descriptive summary for age and BMI, overall and according to treatment assignment (N pts randomized, N missing values, mean, SD, min, Q1, median Q3, max)

2.6.5 Primary Efficacy Analysis

The primary efficacy analysis will proceed as summarized in Section 2.5 above. The data cut-off and database lock dates used for the analyses and the median follow-up duration (see §2.4) will be reported (MFU overall and also by treatment group).

2.6.5.1 Models

Stratified Cox PH regression models will be used to: estimate HRs (95% CI) for treatment effect, unadjusted for covariates and stratified log-rank test statistic and p-value; and estimate HRs (95% CI) for treatment effect within subgroups by including treatment-by-covariate interaction in the model.

2.6.5.2 Sensitivity and Subgroup Analyses

1) Primary efficacy analysis test and HR (CI) estimates will be re-estimated, with each of the two stratification factors as the only stratification factor for the model and with both (6 strata).

2) Subgroup analysis planned per protocol was according to prior chemotherapy use (yes/no); HRs and CIs will be reported for subgroups defined by actual prior therapy (no prior CT/ET, prior

CT±ET, and prior ET only), and a new variable also incorporating whether prior ET included CDK4/6 inhibitor.

2.6.5.3 Tables and Figures

- KM plot of distribution of TTF, x-axis in months by 3-monthly intervals until max of 24 mos; x-axis labeled as 'Months from randomization' and y-axis labeled as 'Percentage free from treatment failure'
- Table of Kaplan-Meier estimates for distribution of TTF according to treatment assignment, including median (95% CI), and 6- and 12- month failure-free % (SE, 95% CI)
- Table of TTF hazard ratio comparing treatment: N pts, N events, median mos w/95% CI (by treatment assignment), stratified Logrank chisq and p-value
- Table of test statistics and HR (95% CI) estimates from sensitivity analysis
- KM plots and estimates, HR (95% CI) estimates in subgroups as described above

2.6.6 Secondary Efficacy Endpoints

Same analysis population as the primary endpoint; also ITT approach.

2.6.6.1 Best overall response and disease control

Disease control will be summarized overall and according to treatment assignment as N (%) with two-sided exact binomial 95% CI, and compared between the two treatment groups using stratified exact CMH test.

Tables:

- Best overall response (CR, PR, SD, PD, NE) as N(%); overall and by measurable/non-measurable only disease status; overall and according to treatment assignment.
- Disease control as N(%); overall and by measurable/non-measurable only disease status; overall and according to treatment assignment
- Disease control will also be summarized according to subgroups

2.6.6.2 Progression free survival (PFS)

PFS analysis will follow that for TTF. The y-axis of KM plot will be "Percentage alive and treatment-free." Estimates also according to subgroups will be provided. Sensitivity analyses will not be conducted, unless indicated from the primary analysis.

2.6.6.3 Overall survival (OS)

OS analysis will follow that for TTF. The x-axis of KM plot will be to max 36 months; y-axis will be "Percentage alive." Estimates also according to subgroups will be provided.

2.6.7 Adverse Events / Safety

The maximum grade of each of 25 targeted AE while on treatment (until EOT visit) will be determined, and the frequencies summarized and tabulated according to grade and treatment assignment, with two-sided exact binomial 95% CIs. The maximum grade, both with and without other grade 3-5 AEs, will also be determined and summarized. The protocol proposed comparisons between treatment groups, but these were omitted as unnecessary except for maximum grade (using stratified exact CMH chi-square test).

In implementation: Because we had some patients with permanent discontinuation (TTF) date wrong (i.e., continuing treatment beyond protocol specification), the primary summary excludes any AEs reported after the revised TTF date. The changes to AE reporting by including the additional cycles after revised TTF will be summarized, including any grade 3+ AEs after the revised permanent discontinuation date will be listed.

The analysis is repeated for the subset of AEs indicated as causality=suspected [as related to protocol treatment(s)].

Note all patients who initiated therapy did initiate the assigned therapy, and thus summaries by treatment assignment reflect actual treatment received.

Tables and listings:

- Targeted AEs max grade throughout treatment (N patients; % of patients) according to treatment assignment
- Patients' maximum AE grade for targeted AEs, according to treatment assignment
- Patients' maximum AE grade for targeted or other grade 3+ reported AE, according to treatment assignment
- N (%) patients experiencing ≥1 targeted AE, by treatment assignment
- N (%) patients experience ≥1 targeted grade 3+ AE (or experiencing ≥1 grade 3+ AE any report), by treatment assignment
- All of the above, for the subset of AEs with causality=suspected
- Listing of AEs after revised TTF date (patid, AE type, max prior to TTF and max all reported cycles) and any grade 3+ AEs after revised TTF date (variables as below)
- Listing of other grade 3-5 AEs, including indicator of causality suspicion and if after revised TTF date (patid, AE type, grade, causality, cycle, indicator if after revised TTF)
- Listing of patients with grade 4 and grade 5 AEs (deaths during treatment) (variables as above); and narratives for grade 5 AEs

2.6.8 Treatment

As noted in §2.3.1, there are a few patients in each treatment group for whom there is an interval of treatment interruption exceeding the protocol specifications. In these cases, the TTF endpoint

variables were redefined. As well, the calculated variables described below only considered the cycles before the revised TTF event date/status.

Variables:

The number of days between randomization and treatment initiation

The last (or latest) cycle number, as well as the reason permanently discontinued treatment.

For VEX: which agent(s) were stopped at TTF date (i.e., all or some)

For paclitaxel: the cumulative number of doses administered (i.e., sum actual d1,d8,d15 doses administered) and cumulative dose administered (i.e., sum actual dose given on d1,d8,e15) prior to TTF were summed across cycles; these were also expressed as relative dose (i.e., denominator is expected number of doses, or total dose, across all cycles initiated).

Dose Modifications indicators are determined for each regimen.

Paclitaxel, indicators created for whether ever dose reduction, ever given off-schedule, and ever dose not given prior to TTF (n.b., for not given, it was meant to indicate skipped dose, so if cycle also indicated permanent discontinuation then it was not counted as skipped). More detailed variables not derived, as other variables will convey this information.

VEX regimens, indicators created for whether ever V,E,X dose modification(s) across cycles prior to TTF were determined:

- V could be <3x/week, 50% dose reduction, or not taken during cycle;
- E could be interruptions >3 days, 50% reduction [every-other-day], or not taken;
- X could be interruptions >3 days, 67% reduction (1 tab bid), or not taken.

In all cases, “not taken” here would indicate an interruption <21 days as described by protocol.

Tables/Figures/Listings:

- Listing of those patients for whom TTF date was revised and differs from eCRF-reported permanent discontinuation date (patid, center code, treatment assignment, rando date (mon/yy), last cycle per eCRF, reported permanent discontinuation date, reported permanent discontinuation reason, revised last cycle corresponding to TTF date, revised TTF date, revised TTF reason)
- Tabulate (N,%) number of cycles, reason permanent discontinuation, for VEX what stopped (all or 1 or 2); by treatment assignment
- Descriptive stats (N, Nmiss, min, max, median, Q1,Q3) number of cycle, by treatment assignment
- Tabulate treatment modifications (N,%), by treatment assignment
- Descriptive stats (N, Nmiss, min, max, median, Q1,Q3) cumulative number of doses and of dose administered, for those assigned paclitaxel