INTERNATIONAL BREAST CANCER STUDY GROUP
IBCSG 42-12/BIG 2-12
SNAP
Schedules of nab-Paclitaxel

A randomized phase II study evaluating different schedules of nab-Paclitaxel in metastatic breast cancer

Amendment 2

EudraCT Number: **2012-003058-10**
NCT Number: **NCT01746225**

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

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Protocol Amendment 2 Signature Page

IBCSG 42-12/BIG 2-12
Schedules of nab-Paclitaxel - SNAP

_____ _____
Date

Approved by:
Group Statistician, International Breast Cancer Study Group
Dr. Meredith M. Regan

_____ _____
Date

Approved by:
Director, International Breast Cancer Study Group
Anita Hiltbrunner

Protocol Amendment 1 Signature Page

IBCSG 42-12/BIG 2-12
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Anita Hiltbrunner

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Date

Principal Investigator Protocol Amendment 2 Signature Page

IBCSG 42-12/BIG 2-12
Schedules of nab-Paclitaxel - SNAP

I have read the amended protocol and agree that it contains all necessary details for conducting this study. I will conduct the study as outlined in the following protocol and in compliance with GCP. I will provide copies of the amended protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by IBCSG, **to all physicians responsible to me who participate in this study. I will discuss this material with them to assure that they are fully informed** regarding the drug and the conduct of the study. I agree to keep records on all patient information, drug shipment and return forms, and all other information collected during the study for a minimum period of 15 years.

Name of Principal Investigator: _____

_____ _____

Signature Date

Principal Investigator Protocol Amendment 1 Signature Page

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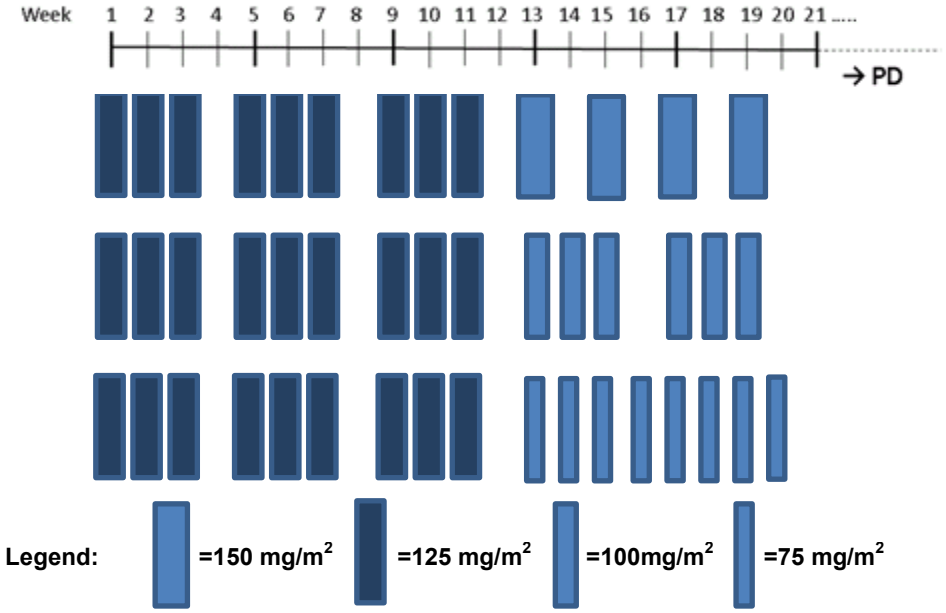
Name of Principal Investigator: _____

_____ _____

Signature Date

Schedules of nab-Paclitaxel - SNAP
Protocol Summary and Schema

A randomized phase II study evaluating different schedules of nab-Paclitaxel in metastatic breast cancer

TITLE	A randomized phase II study evaluating different schedules of nab-Paclitaxel in metastatic breast cancer (SNAP Trial)
SPONSOR	International Breast Cancer Study Group (IBCSG)
PHARMA PARTNER	Celgene
POPULATION	Patients with histologically or cytologically confirmed HER2-negative metastatic (stage IV) breast cancer who have not received chemotherapy for metastatic breast cancer.
STUDY SCHEMA	RANDOMIZE → A: nab-Paclitaxel 125 mg/m^2 days 1,8,15 3 cycles (28-day) → A: nab-Paclitaxel 150 mg/m^2 days 1, 15 RANDOMIZE → B: nab-Paclitaxel 125 mg/m^2 days 1,8,15 3 cycles (28-day) → B: nab-Paclitaxel 100 mg/m^2 days 1,8,15 RANDOMIZE → C: nab-Paclitaxel 125 mg/m^2 days 1,8,15 3 cycles (28-day) → C: nab-Paclitaxel 75 mg/m^2 days 1,8,15,22 Schedule of nab-Paclitaxel administration:  Continue treatment until progressive disease (PD) or unacceptable toxicity.
RANDOMIZATION	Patients will be randomized (using a 1:1:1 allocation) to one of three treatment arms.

RATIONALE	Longer first line chemotherapy duration has recently been associated with a modest, but significant improvement in overall survival and a clinically meaningful and statistically significant improvement in progression-free survival, in metastatic breast cancer patients (1). Prolonging chemotherapy until disease progression, however, must be weighed against the detrimental effects of continuous chemotherapy delivery. The SNAP trial seeks to improve the tolerability of prolonged chemotherapy administration strategy by studying alternative treatment schedules, while preserving and possibly improving treatment efficacy in this disease setting. The availability of a new nanoparticle albumin-bound taxane, nab-Paclitaxel (Abraxane®), represents an opportunity to test this hypothesis. Nab-Paclitaxel has been developed in an attempt to reduce the toxicity associated with standard taxane administration (caused by the use of chemical solvents) while increasing antitumor efficacy. FDA and EMEA approval was based on a Phase III study (N=454) reporting that patients treated with nab-Paclitaxel (260 mg/m^2 every 3 weeks) achieved significantly higher response rates and longer PFS compared with standard 3-weekly paclitaxel (2). More recently, a randomized study in first-line metastatic breast cancer demonstrated superior efficacy and safety of nab-Paclitaxel 150 mg/m^2 on a weekly schedule, compared with docetaxel 100 mg/m^2 every 21 days, with a statistically and clinically significant prolongation of PFS and OS. Toxicity increased, however, particularly in terms of neutropenia and neurotoxicity, and only 50% of the patients were able to receive the planned chemotherapy cycles. Conversely, the weekly 100 mg/m^2 nab-Paclitaxel schedule showed a good tolerability profile with a moderate incidence of grade 3 peripheral neuropathy and, as evaluated by the independent reviewers, also significantly prolonged PFS (> 5 months) compared with docetaxel (3,4). The SNAP randomized phase II trial evaluates three schedules of nab-Paclitaxel as prolonged chemotherapy administration strategy. Each of three arms will be compared to a historical reference of seven-month median PFS based on the most recent trial with docetaxel as control arm (3) to determine whether any of the three arms are worthy of further investigation. In the original design of this phase II trial, patients will receive three cycles of nab-Paclitaxel 150 mg/m^2 days 1, 8, 15 every 28 days during induction phase. Following the first safety review of 48 treated patients, it was decided to modify the dose in the induction phase to 125 mg/m^2.
QUALITY OF LIFE/ TRANSLATIONAL RESEARCH	Quality-of-life assessments will be conducted to explore the change in QL over time until treatment discontinuation by LASA scales for physical well-being, mood, coping effort, overall treatment burden, appetite, tiredness, hair loss and feeling sick (nausea/vomiting). Sensory neuropathy will be assessed by the 4-item subscale of the FACT/GOG-Ntx. Translational research will investigate the prognostic role of putative markers SPARC and caveolin determined in FFPE tumor tissue.
ELIGIBILITY	**Inclusion criteria** • Histologically or cytologically confirmed HER2-negative metastatic (stage IV) breast cancer. • Measurable or non-measurable, but radiologically evaluable, 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.
- Either ER-positive or ER-negative disease. Patients with ER-positive disease must be endocrine resistant, defined as having failed at least one prior endocrine therapy for breast cancer, or must be candidates for first-line chemotherapy.
- If previously treated with a taxane or anthracycline 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. Must meet all criteria: absolute neutrophil count ≥ 1500/mm^3 (1.5 x 10^9/L), platelets ≥ 100 x 10^9/L and 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 and Gault formula).
- Normal liver function. Must meet all criteria: ALT (SGPT) and AST (SGOT) ≤ 3 × upper limit of normal (ULN) (without liver metastases; total bilirubin ≤ 1.5 mg/dL;. Exceptions: If the patient has liver metastases, ALT (SGPT) and AST (SGOT) must be ≤ 5 × ULN; total bilirubin ≤ 1.5 mg/dL. If the patient has Gilbert's disease higher bilirubin is acceptable (≤ 3 mg/dL)
- Normal cardiac function defined as left ventricular ejection fraction within the institutional range of normal as measured by MUGA or echocardiogram.
- Women of child bearing potential must have documented negative pregnancy test within 2 weeks prior to randomization and agree to acceptable birth control during the duration of the trial therapy and for a period of 6 months following the last administration of study drug. If for any reason the administration of first dose of trial treatment is not within 2 weeks of the pregnancy test, a second pregnancy test should be performed within two weeks of day 1 of cycle 1.
- Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to randomization.
- Completed baseline Quality of Life Form.
- The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.
- Availability of an FFPE block from the primary tumor (breast lesion) for submission to central pathology review and for translational research.
- Written consent to pathology material submission, indicating the patient has been informed of and agrees to tissue material use, transfer and handling, must be signed and dated by the patient and the Investigator prior to randomization.

Exclusion criteria

- Any prior chemotherapy for metastatic breast cancer.
- Presence of CNS metastasis.
- Peripheral neuropathy grade 2 or higher (CTCAE version 4).
- Significant uncontrolled cardiac disease (i.e. unstable angina, recent 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 study medication or excipients. • The use of any anti-cancer investigational agents within 30 days prior to expected start of trial treatment. • Inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator.

STUDY OBJECTIVES AND ENDPOINTS	**Primary objective**
	To evaluate the efficacy of three different schedules of nab-Paclitaxel administration, as measured by progression-free survival (PFS), using the historical reference of PFS of docetaxel for first-line treatment of metastatic breast cancer.
	Secondary objectives
	• To evaluate:
	  • Tolerability
	  • Feasibility
	  • Disease response according to RECIST criteria, including disease control rate
	  • Overall survival
	• To explore the changes in quality of life (QL) over time until treatment discontinuation.
	• To investigate the prognostic role of putative markers (SPARC and caveolin) and assess any change in the expression of SPARC and caveolin between primary and the metastatic sites.
	Primary endpoint
	• Progression-free survival (PFS): time from randomization to documented progressive disease according to RECIST criteria or death, whichever occurs first.
	Secondary endpoints
	• Tolerability: adverse events according to CTCAE v4
	• Feasibility: completing treatment according to the protocol for at least 24 weeks
	• Disease control: overall response or stable disease (or non-CR/non-PD for patients with non-measurable disease) or better (i.e., partial or complete response) according to RECIST criteria for a duration of ≥24 weeks
	• Overall survival: time from randomization to death from any cause
	• QL: primary endpoint physical well-being
	• Prognostic markers: SPARC and caveolin expression

STRATIFICATION	Stratification will be performed according to: • ER Status (positive or negative) • Prior adjuvant taxanes (yes or no) • Measurable or non-measurable only disease according to RECIST criteria Dynamic institution balancing will be done in order to balance randomized assignments within institution.

STATISTICAL CONSIDERATIONS	The primary efficacy endpoint of PFS will be evaluated among each of the three treatment arms separately, in three independent tests, and compared to the historic PFS of first-line docetaxel. Assuming the median PFS of docetaxel is 7 months and the median PFS of a new regimen is 10 months, with 76 patients in an arm, and an accrual rate of 8 patients per month for an accrual period of 30 months plus an additional 16 to 18 months of follow up to reach the target number of events, the study will have 88% power to detect an improvement in PFS in a new regimen relative to docetaxel, using a one-sample log-rank test at the one-sided significance level of 0.05. The target number of events per group is 63. Assuming a 12% drop out rate and those patients do not contribute events, the sample size is increased to 86 patients per arm. Randomized patients who received at least one dose of the trial treatment will be included in the PFS analysis. For each arm separately, PFS distributions will be summarized using the method of Kaplan-Meier and the two-sided 90% confidence interval (CI) for the median PFS will be provided. The toxicities and feasibility of each of the three treatment arms will be assessed. OS, disease control rate and other measures of disease response will be evaluated for each treatment arm separately. The primary quality of life endpoint is physical well-being. The change in QL over time until treatment discontinuation for patients on each arm will be explored using repeated measures modeling. In translational research, on FFPE material from the primary tumor and metastatic sites separately, it will be evaluated whether SPARC and caveolin are prognostic markers for PFS in women with metastatic breast cancer using log-rank tests and Cox regression analysis.
NUMBER OF PATIENTS	258 patients will be enrolled. (Arm A: 86, Arm B: 86, Arm C: 86)
STUDY DURATION	Randomization of 258 patients during approximately 24 to 26 months, with an additional 16 to 18 months of follow up after the last patient is entered, to reach the target number of events.
REFERENCES FOR SYNOPSIS	1. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: A systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 29: 2144-2149, 2011. 2. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23: 7794-7803, 2005. 3. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-Paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 27:3611-3619, 2009. 4. Gradishar WJ, Krasnojon D, Cheporov S, et al. Phase II Trial of Nab-Paclitaxel Compared With Docetaxel as First-Line Chemotherapy in Patients With Metastatic Breast Cancer: Final Analysis of Overall Survival. Clin Breast Cancer. 2012 Oct; 12(5):313-21.

Trial Schedule	Within 14 days prior to rando	Induction Cycle 1 (28 days)			Induction Cycle 2 (28 days)			Induction Cycle 3 (28 days)			Maintenance Cycles 4 and up (to PD or stop tx)				Within 30 days after end of tx	Follow up to PD	Follow after PD
Days during cycle		1	8	15	1	8	15	1	8	15	1	8	15	22			
Informed consent	X																
Medical history	X																
Physical exam	X	X			X			X			X				X		
Vital signs [1)]	X	X			X			X			X				X		
Height	X																
ECOG PS	X	X			X			X								X	X
MUGA or echocardiogram	X[14)]				X[14)]			X[14)]			X[14)]				X[14)]		
HER2 / ER / PgR status	X																
Hematology [2)]	X	X	X	X	X	X	X	X	X	X	X	B & C	X	C	X		
Biochemistry [3)]	X	X			X			X			X				X		
Baseline symptoms	X																
Concomitant medications	X	X[13)]			X			X			X				X		
Pregnancy test	X	X[4)]															
Eligibility criteria	X																
QL self-assessment [5)]	X [7)]	X[7)]			X			X			X				X		
Tumor evaluation [6)]	X	.....every 12 weeks until progression													X[8)]	X[8)]	
FFPE sample from primary tumor [9)]	X																
FFPE sample metastatic biopsy [9)]	X																
Nab-paclitaxel administration [10)]		X	X	X	X	X	X	X	X	X	X	B & C	X	C			
Adverse events [11)]					X			X			X				X [12)]		
Survival status																X	X

B = required for arm B; C = required for arm C

1) Blood pressure and pulse rate after 5 minutes in sitting position; body temp.; body weight; respiratory rate
2) Hemoglobin, ANC, platelets
3) ALT (SGPT), AST (SGOT), total bilirubin, serum creatinine or calculated creatinine clearance acc. Cockcroft and Gault
4) Pregnancy test (in case of childbearing potential) to be repeated prior to cycle 1 if more than 14 days from pre-randomization test to date of first dose of cycle 1.
5) Complete QL at baseline (after informed consent and prior to randomization) and on day 1 of the first 12 cycles, before any diagnostic or treatment intervention; or until treatment discontinuation, whichever occurs first.
6) Tumor evaluation to be done according to RECIST 1.1 criteria every 12 weeks (see Section 10.4). For bone scans see note c) in "Notes for Sections 10.1.-10.4." in section 10.4.
7) May be within 28 days prior to randomization If the baseline QL was completed within 14 days prior to treatment start, no QL form is required at day 1 of cycle one.
8) If PD not documented, tumor evaluation must be repeated at end of treatment visit and every 12 weeks (+/- 2 weeks) until PD
9) Availability of FFPE block from primary tumor is eligibility criterion; in case of metastatic biopsy FFPE block to be submitted (see section 13.2)
10) For dosing of nab-Paclitaxel, see section 7.1.3
11) Adverse events must be reported for the cycle in which they occur
12) Adverse events must be recorded during and up to 30 days after stop of treatment
13) Concomitant medication eCRFs should be completed continuously as medications are started or re-started.
14) Baseline MUGA/echo can be done up to 6 months prior to randomization if patient is clinically cardiac compensated with no heart symptoms. During and at end of treatment, repeat if clinically indicated.

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APPENDICES

I. Requirements for Informed Consent
II. NCI Common Terminology Criteria for Adverse Events v4 [available from the internet at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html]

1. Background and rationale

1.1. Disease background

Metastatic breast cancer is an incurable disease, but can be successfully managed with appropriate treatment strategies (1,2,3,4). The aims of therapy in this setting include prolongation of survival with good quality of life and symptom palliation. Because of the chemosensitivity of this disease, the large majority of patients are, or eventually become, candidates for chemotherapy, either upfront in endocrine-insensitive or after failure of hormone therapy in endocrine-sensitive disease.

Although the selection of chemotherapy is generally affected by patient and disease-related factors, as well as patient/physician preferences, controversy remains about how long chemotherapy should be continued, and the number of administered cycles is generally based on patient responsiveness and individual tolerability as well as physician preferences.

During the last three decades, a number of randomized clinical trials have addressed the value of maintenance first-line chemotherapy in metastatic breast cancer. These studies indicated that prolonged treatment results in a longer time to progression and improved quality of life, but failed to show a consistent benefit in terms of overall survival (OS) for patients who continued chemotherapy. However, some of these early studies were plagued by a number of limitations, such as insufficient sample size, limited chemotherapy duration in control arms, and/or drugs and schedules that, based on today standards, can be considered obsolete (5).

A recently published systematic review including 11 randomized controlled trials (6,7,8,9,10,11,12,13,14,15,16), comparing shorter with longer chemotherapy duration, showed that longer duration is associated with a modest, but significant improvement in OS and a clinically meaningful and statistically significant improvement in progression-free survival (PFS) (17). The formal demonstration of a survival advantage associated with longer chemotherapy use has clinical and scientific consequences. From a clinical viewpoint, prolonged chemotherapy administration may now be justified on the basis of the possibility of an appreciable survival benefit for some patients. From a scientific perspective, this finding supports further research on maintenance therapy in metastatic breast cancer.

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, with lower dosages, could be explored in this disease setting.

1.2. Nab-Paclitaxel

The availability of a new nanoparticle albumin-bound taxane, nab-Paclitaxel (Abraxane®), represents an opportunity to test this hypothesis.

Nab-Paclitaxel has been developed in an attempt to reduce the toxicity associated with standard taxane administration (caused by the use of chemical solvents) while increasing

antitumor efficacy. Conventional taxane formulations use solvents (e.g., Cremophor EL (polyoxyethylated castor oil) for paclitaxel and Tween 80 for docetaxel) to overcome the insolubility of the drug molecules. These solvents are associated with increased toxicity as hypersensitivity reactions, neurotoxicity and additional myelosuppression, and may also hinder the ability of circulating drug to cross the endothelial barrier and accumulate in tumors, reducing antitumor activity and increasing the risk of systemic toxicity. The first attempt to overcome the limitations imposed by solvent use was the development of albumin-bound (nab)-paclitaxel. With nab-Paclitaxel, the reversible binding of albumin to paclitaxel permits exploitation of endogenous albumin pathways to enhance delivery of the drug to tumors. Albumin is a natural carrier for hydrophobic molecules (18,19) and binds to the gp60 receptor on endothelial cells, signaling the formation of vesicles (caveolae) in the membrane that carry the albumin complex across the endothelial membrane (transcytosis) and into surrounding tissue. The entry and retention of albumin complexes in tumor tissue are facilitated by the enhanced permeation and retention effect, i.e., the accumulation of albumin complexes and other macromolecules in the tumor interstitium via leaky tumor vasculature coupled with reduced release back into blood vessels due to impaired lymphatic drainage in tumor tissue. The preferential accumulation of albumin-bound drug in the tumor interstitium results in high concentrations of active drug being in contact with tumor cells. This process appears to be facilitated by the albumin-binding activity of secreted protein acidic and rich in cysteine (SPARC, also known as osteonectin) (20), a protein with multiple biologic activities including roles in embryonic development, wound repair and tissue remodeling. SPARCs are overexpressed in many tumor types including breast cancer, and high SPARC expression is associated with a significantly poorer outcome in breast cancer (21).

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of nab-Paclitaxel at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2653 to 16736 µg·h/mL following dosing from 80 to 300 mg/m^2. Following intravenous administration of nab-Paclitaxel to patients with metastatic breast cancer at the recommended clinical dose of 260 mg/m^2, paclitaxel plasma concentrations declined in a multiphasic manner. The mean C_{max} of paclitaxel, which occurred at the end of the infusion, was 18.7 µg/mL. The mean total clearance was 15 L/h/m^2. The terminal half-life was about 27 hours. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a study in patients with advanced solid tumors, the pharmacokinetic characteristics of paclitaxel following nab-Paclitaxel administered intravenously at 260 mg/m^2 over 30 minutes were compared with those following 175 mg/m^2 of the solvent-based paclitaxel injection administered over 3 hours. The clearance of paclitaxel with nab-Paclitaxel was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In a repeat dose study with 12 patients receiving nab-Paclitaxel administered intravenously at the approved dose, intrapatient variability in systemic paclitaxel exposure (AUCinf) was 19% (range = 3.21%-27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses. An analysis of patient exposure (AUCinf) against bodyweight

indicated a trend toward reduced AUC at 260 mg/m^2 nab-Paclitaxel, with decreased body weight. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.

The protein binding of paclitaxel following nab-Paclitaxel was evaluated by ultrafiltration. The fraction of free paclitaxel was significantly higher with nab-Paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%), resulting in significantly higher exposure to unbound paclitaxel with nab-Paclitaxel compared with solvent-based paclitaxel, even though the total exposure is comparable. This higher exposure is possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. Based on the published literature, in vitro studies of binding to human serum proteins, (using paclitaxel at 6µM) the presence of ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel (22,23).

1.3. Nab-Paclitaxel clinical data

A phase I clinical study by Ibrahim (24) conducted on 19 patients with solid tumors including breast cancer, showed a maximum tolerated dose of nab-Paclitaxel about 70% higher than that of solvent-based paclitaxel formulation (300 mg/m^2 for an every 3 weeks regimen). Dose-limiting toxicities were sensory neuropathy, stomatitis and ocular toxicity (superficial keratopathy and blurred vision at a dose of 375 mg/m^2). No patients experienced hypersensitivity reactions. Nab-paclitaxel was administered intravenously with no premedication, in a relatively short infusion period (30 minutes versus 3 hours for solvent- based paclitaxel) and with a standard infusion device. Moreover, pharmacokinetic parameters showed a linear trend. A Phase II trial confirmed that nab-Paclitaxel has important antitumor activity in patients with metastatic breast cancer. The overall response rate (at a dose of 300 mg/m^2 every 3 weeks) was 48% for all patients and 64% for patients in first-line therapy. Median time to tumor progression was 26.6 weeks for all patients and 48.1 weeks for patients with confirmed tumor responses; median OS was 63.6 weeks. No severe ocular events were noted, and other common taxane-associated toxicities were less frequent and less severe (e.g., myelosuppression, peripheral neuropathy, nausea, vomiting, fatigue, arthralgia, myalgia, alopecia) (25). In a phase III trial, 460 women with measurable metastatic breast cancer who had no prior taxane therapy for metastatic disease were randomized to receive either conventional paclitaxel (175 mg/m^2 every 3 weeks via 3-hour infusion; N=225) with standard premedication with dexamethasone and antihistamines or nab-Paclitaxel (260 mg/m^2 q3w via 30-minute infusion; N=229) with no standard premedication (26). Approximately three quarters of patients had received prior anthracycline therapy, and more than half of patients had received at least one prior treatment for metastatic disease. The response rate was 33% with nab-Paclitaxel versus 19% with paclitaxel (P= 0.001). The time to disease progression (TTP) was significantly prolonged with nab-Paclitaxel, from a median of 16.9 weeks to 23 weeks (Hazard Ratio= 0.75; P= 0.006). There was no significant difference between groups with regard to OS among all patients (65.0 vs 55.7 weeks; P= 0.374).

With regard to toxicities, nab-Paclitaxel was associated with a significantly reduced frequency of grade 3-4 neutropenia. Sensory neuropathy of any grade was significantly more common with nab-Paclitaxel. Of 24 patients with grade 3 neuropathy; 14 had documented rapid improvement (median 22 days) with 10 of these patients resuming treatment at a reduced dose. Overall, 6 of 233 patients (3%) discontinued nab-Paclitaxel

due to sensory neuropathy; there were no cases of severe motor neuropathy. Despite the absence of premedication in the nab-Paclitaxel group, hypersensitivity reactions were virtually absent (grade 2 in less than 1% of patients). Overall adverse event rates in each group did not differ from patients aged < 65 years and those aged ≥ 65 years, raising no additional safety concerns about the use of nab-Paclitaxel in older patients. Similar findings were recently reported in a Chinese trial comparing solvent-based paclitaxel (175 mg/m^2) and nab-Paclitaxel (260 mg/m^2 q3w) in 210 patients with metastatic breast cancer (27).

In a trial comparing weekly nab-Paclitaxel, every three-weekly (q3w) nab-Paclitaxel and conventional docetaxel in first-line treatment for metastatic breast cancer, 302 patients were randomized to receive 300 mg/m2 of nab-Paclitaxel q3w (N=76), 100 mg/m2 of nab-Paclitaxel weekly 3 of 4 weeks (N= 76), 150 mg/m2 weekly 3 of 4 weeks (N= 74) or 100 mg/m2 of docetaxel q3w (N=74) (28,29). The objectives of the trial were to obtain comparative toxicity and preliminary antitumor response data for nab-Paclitaxel versus docetaxel, weekly versus q3w nab-Paclitaxel, and higher dose versus lower dose weekly nab-Paclitaxel. Nab-paclitaxel 150 mg/m2 weekly demonstrated significantly longer PFS than docetaxel by both independent radiologist assessment (12.9 v 7.5 months, respectively; P=0.0065) and Investigator assessment (14.6 v 7.8 months, respectively; P=0.012). It should be noted that the weekly 100 mg/m2 nab-Paclitaxel schedule, as evaluated by the independent reviewers, also significantly prolonged PFS (> 5 months) compared with docetaxel. With regard to toxicity, Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms, with the nab-Paclitaxel 100 mg/m2 weekly regimen being associated with a significantly lower rate than the nab-Paclitaxel q3w regimen. The frequency and grade of peripheral neuropathy were similar in all arms. Febrile neutropenia occurred in 1% of each of the nab-Paclitaxel groups compared with 8% of the docetaxel group. Rates of neutropenia were significantly higher with q3w nab-Paclitaxel and the 150mg/m2 weekly dose compared with the 100mg/m2 weekly dose. The rate of peripheral neuropathy was significantly lower in the 100mg/m2 weekly nab-Paclitaxel group than in the other nab-Paclitaxel groups. The median time to improvement of peripheral neuropathy was 16 days in the nab-Paclitaxel q3w group, 22 days in the 100mg/m2 weekly nab-Paclitaxel group, 23 days in the 150mg/m2 weekly nab-Paclitaxel group and 41 days in the docetaxel group. This trial showed that in first-line treatment two regimens of nab-Paclitaxel (150 mg/m2 weekly and 300 mg/m2 q3w) increase PFS compared with docetaxel with an improved safety profile.
Moreover, the 150 mg/m2 weekly schedule proved to be superior to docetaxel in terms of overall survival (28).

Based on this most-recent trial with docetaxel as the control arm (28), a seven-month median PFS was selected as a historical reference to which each of the three different schedules of nab-Paclitaxel administration will be compared in the SNAP trial to determine whether any of the three schedules are worthy of further investigation.

1.4. Trial rationale

With these premises, we designed a phase II randomized clinical trial evaluating three treatment schedules, each consisting of an induction and a maintenance phase of nab-Paclitaxel, for the strategy of prolonged administration of first-line chemotherapy for metastatic breast cancer. The aim of the alternative schedules is to improve the tolerability

of prolonged chemotherapy administration while preserving and possibly improving treatment efficacy.

Patients will be randomized to one of three treatment arms and continue treatment until disease progression or unacceptable toxicity.

In the original design, in the induction phase, the schedules each begin with 3 cycles of nab-Paclitaxel 150 mg/m^2 days 1, 8, 15 every 28 days. The 150mg/m^2 regimen has demonstrated a survival advantage compared with conventional docetaxel (28). However, by limiting its administration to 3 cycles, this should improve tolerability and ability to continue treatment, as most cumulative toxicity leading to treatment discontinuation occurred after 3-4 cycles (28). The first safety review of the induction phase of the regimen, conducted in March 2014 on 48 patients, revealed however, that few patients completed the three cycles of induction regimen without dose modification. The median of actually administered doses corresponds to a dose level of about 125 mg/m² given 3 out of 4 weeks. It was therefore decided to modify the dose in the induction phase to 125 mg/m² days 1, 8, 15 every 28 days.

The schedules continue into a maintenance phase from cycle 4 and through subsequent cycles using one of three alternative dose densities using lower dosages which each give a cumulative dose of 300 mg/m^2 over 28 days (schema, Section 3.1).

Because the aim of the treatment schedules is prolonged treatment, during the first 3 cycles and during all subsequent cycles, the protocol provides strict dose-reduction criteria in case of thrombocytopenia, neutropenia, anemia, febrile neutropenia, neurotoxicity, and other grade 3-4 toxicities.

2. Trial objectives

2.1. Primary objective

To evaluate the efficacy of three different schedules of nab-Paclitaxel administration, as measured by progression-free survival (PFS), using the historical reference of PFS of docetaxel for first-line treatment of metastatic breast cancer.

2.2. Primary endpoint

Progression-free survival (PFS) is defined as time from randomization to documented progressive disease according to RECIST criteria (Section 9) or death, whichever occurs first. A detailed definition is given in section 9.12.

2.3. Secondary objectives

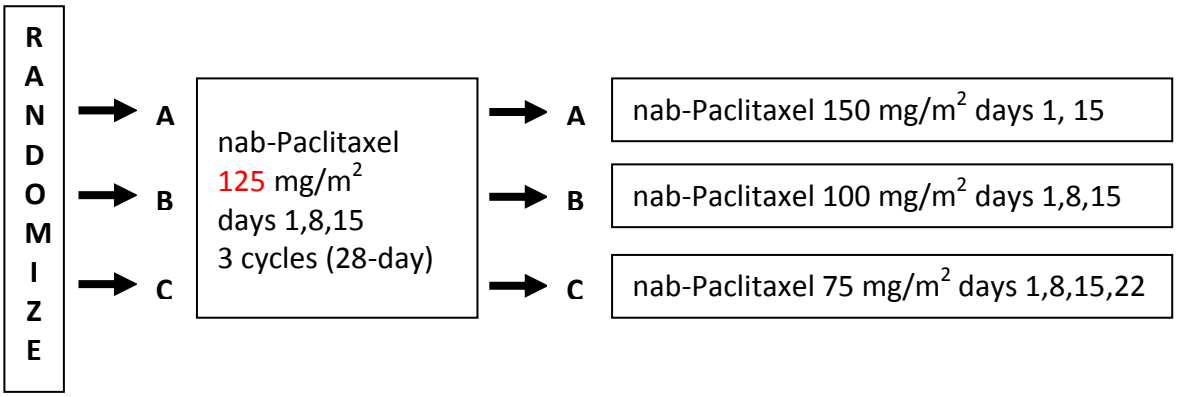
- To evaluate:
  - Tolerability
  - Feasibility
  - Disease response according to RECIST criteria (Section 9), including disease control rate (DCR)
  - Overall survival (OS)
- To explore the changes in quality of life (QL) over time until treatment discontinuation.
- To investigate the prognostic role of putative markers (SPARC and caveolin) and assess any change in the expression of SPARC and caveolin between the primary and the metastatic sites.

2.4. Secondary endpoints

- Tolerability: adverse events according to CTCAE version 4
- Feasibility: completing treatment according to the protocol for at least 24 weeks
- Disease control: overall response of stable disease (or non-CR/non-PD for patients with non-measurable disease) or better (i.e., partial or complete response) according to RECIST criteria for a duration of ≥24 weeks
- Overall survival: time from randomization to death from any cause
- QL endpoints (see Section 14.2)
- Prognostic marker endpoints (see Section 13.4)

3. Trial design and duration

3.1. Trial schema



Randomization allocation 1:1:1

- nab-Paclitaxel administered in 28-day cycles
- Continue treatment until progressive disease (PD) or unacceptable toxicity.
- 258 (Arm A 86, Arm B 86, Arm C 86) patients will be randomized.
- Tumor evaluations will be required every 12 weeks.

3.2. Trial duration

The randomization of 258 patients is expected to occur over approximately 24 to 26 months, with an additional 16 to 18 months of follow up after the last patient is randomized. The end of the trial therefore will be approximately 4 years after randomization of the first patient.

All patients will be followed up until approximately 18 months following the enrollment of the last patient to reach the target number of events (maximum of 42 months, minimum of approximately 18 months).

If at the end of the trial a patient has not progressed and wants to continue nab-Paclitaxel, the agent will be provided until progressive disease. In this case, adverse events, serious adverse events, treatment, and concomitant medications will continue to be collected.

4. Patient selection: criteria for patient eligibility/ineligibility

4.1. Inclusion criteria

4.1.1. Histologically or cytologically confirmed HER2-negative metastatic (stage IV) breast cancer.

4.1.2. Measurable or non-measurable, but radiologically evaluable, disease according to RECIST 1.1 criteria.

4.1.3. Female aged 18 years or older.

4.1.4. Life expectancy > 3 months.

4.1.5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

4.1.6. Either ER-positive or ER-negative disease. Patients with ER-positive disease must be endocrine resistant, defined as having failed at least one prior endocrine therapy for breast cancer, or must be candidates for first-line chemotherapy.

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

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

4.1.9. Normal hematologic status. Must meet all criteria: absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5 x 10^9/L), platelets ≥ 100 x 10^9/L and hemoglobin (Hgb) ≥ 9 g/dL (≥ 90 g/L).

4.1.10. Normal renal function (serum creatinine ≤ 1.5 ULN or calculated creatinine clearance ≥ 50mL/min according to the Cockcroft and Gault formula).

4.1.11. Normal liver function. Must meet all criteria: ALT (SGPT) and AST (SGOT) ≤ 3 × upper limit of normal (ULN)(without liver metastases); total bilirubin ≤ 1.5 mg/dL. Exceptions: If the patient has liver metastases, ALT (SGPT) and AST (SGOT) must be ≤ 5 × ULN; total bilirubin ≤ 1.5 mg/dL. If the patient has Gilbert's disease higher bilirubin is acceptable (≤ 3 mg/dL).

4.1.12. Normal cardiac function defined as left ventricular ejection fraction within the institutional range of normal as measured by MUGA or echocardiogram

4.1.13. Women of child bearing potential must have documented negative pregnancy test within 2 weeks prior to randomization and agree to acceptable birth control during the duration of the trial therapy and for a period of 6 months following the last administration of study drug. If for any reason the administration of first dose of trial treatment is not within 2 weeks of the pregnancy test, a second pregnancy test should be performed within two weeks of day 1 of cycle 1.

4.1.14. Written Informed Consent (IC) must be signed and dated by the patient and the Investigator prior to randomization.

4.1.15. Completed baseline Quality of Life Form.

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

4.1.17. Availability of an FFPE block from the primary tumor (breast lesion) for submission to central pathology review and for translational research.

4.1.18. Written consent to pathology material submission, indicating the patient has been informed of and agrees to tissue material use, transfer and handling, must be signed and dated by the patient and the Investigator prior to randomization.

4.2. Exclusion criteria

4.2.1. Any prior chemotherapy for metastatic breast cancer.

4.2.2. Presence of CNS metastasis.

4.2.3. Peripheral neuropathy grade 2 or higher (CTCAE version 4).

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

4.2.5. Pregnant or lactating.

4.2.6. 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).

4.2.7. 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.

4.2.8. Contraindications or known hypersensitivity to the study medication or excipients.

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

4.2.10. Inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator.

5. Randomization and Stratification

This trial will use the web-based IBCSG Registration/Randomization System. Each Participating Group will determine how its Participating Centers will access the IBCSG Registration/Randomization system, either through a Group Randomization Center, or directly from the Participating Center. The following procedures should be used in either case. Country- or Group-specific details for registering/randomizing can be found in the "IBCSG Group/Country Specific Logistical Information," which is available from IBCSG.

5.1. Randomization procedures

Complete the following steps to randomize a patient on this trial.

5.1.1. Verify eligibility

5.1.2. Obtain written informed consent both for the clinical trial and the pathology material submission, signed and dated by the patient and Investigator. Informed consent must be obtained prior to any trial-specific screening procedure or intervention.

5.1.3. Directly access the IBCSG Registration/Randomization System and provide the requested information as indicated on the Confirmation of Registration (42-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 e-mail:

- Patient ID (randomization number)
- Treatment assignment
- Date of randomization

5.1.4. Submit the Confirmation of Randomization (42-A) electronic case report form (eCRF) via iDataFax. The patient binder of eCRFs will be available in iDataFax within 24 hours of successful randomization.

5.2. Randomization help desk

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

Business Hours: 00:00 (midnight) to 18:00 US Eastern Time Monday through Friday

FSTRF Randomization Help Desk
Frontier Science & Technology Research Foundation (FSTRF)
4033 Maple Rd, Amherst, NY 14226 USA
Phone: +1 716 898 7301
Fax: +1 716 898 7082
Email: bc.helpdesk@fstrf.org

This telephone information may also be used after business hours for urgent issues.

5.3. Randomization assignment

Randomization is performed prior to starting any nab-Paclitaxel. Patients are assigned randomly to one of 3 treatment schedules in a ratio of 1:1:1.

All three treatment schedules begin with the same chemotherapy dosing schedule:

A, B, C: nab-Paclitaxel 125 mg/m^2 days **1, 8, 15** every 28 days for 3 cycles

And during the fourth and subsequent cycles continue treatment with an alternative maintenance dosing schedule:

A: nab-Paclitaxel 150 mg/m^2 days 1, 15 every 28 days
B: nab-Paclitaxel 100 mg/m^2 days 1, 8, 15 every 28 days
C: nab-Paclitaxel 75 mg/m^2 days 1, 8, 15, 22 every 28 days

5.4. Stratification

For randomization, patients will be stratified by

- ER status (ER-negative or ER-positive) based on metastatic biopsy if available or otherwise the primary tumor
- Prior adjuvant taxanes in the neoadjuvant or adjuvant setting (yes or no)
- Measurable or non-measurable only disease according to RECIST criteria.

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

6. Study drugs formulation and handling

Nab-Paclitaxel is the investigational drug used in this trial. Celgene Corporation will supply nab-Paclitaxel for the entire duration of the study. Please consult the Drug Supply Manual for further details on initial supply and resupply procedures.

Complete details of the study drug logistics, distribution, packaging, labeling and handling are described in a separate drug supply manual.

6.1. nab-Paclitaxel

6.1.1. Product characterization

Nab-Paclitaxel is a solvent-free, protein-bound particle form of paclitaxel injection with a mean particle size of approximately 130 nanometers. Nab-Paclitaxel is supplied as a white-to-yellow, sterile, lyophilized cake containing 100 mg of paclitaxel and approximately 900mg (800 mg theoretical) of human albumin solution as a stabilizer in a 50-mL vial. Each vial of the lyophilized product is reconstituted with 20 mL of 0.9% Sodium Chloride Injection (USP) to create a suspension. Each mL of reconstituted suspension contains 5 mg of paclitaxel. Vials of nab-Paclitaxel provided for clinical trials are labeled according to country-specific regulatory requirements for labeling of investigational products. Nab-Paclitaxel contains paclitaxel, a taxane with the Anatomical Therapeutic Chemical (ATC) code L01C D01.

6.1.2. Pharmaceutical form

Nab-Paclitaxel - powder for suspension for infusion - will be supplied in vials and each vial contains 100 mg of paclitaxel (as paclitaxel albumin).

After reconstitution, each mL of suspension contains 5 mg of paclitaxel (as paclitaxel albumin).

Excipients: the reconstituted medicinal product contains approximately 425 mg sodium per dose.

6.2. Packaging and labeling

Nab-Paclitaxel is supplied as a sterile, lyophilized powder for reconstitution before use. Both the box label and vial label will fulfill all requirements specified by governing regulations.

All drugs will be stored as per the current version of the products SPC's (Summary of Product Characteristics) and the standard hospital procedures. Unopened vials do not require any special temperature storage conditions (Store the vials in original cartons to protect from light, below 25°C). Pharmacy will maintain temperature logs of all storage conditions as per hospital pharmacy standard operating procedures.

Celgene will ship the investigational product to the pharmacy at each study site. Each vial will be packed into a white cardboard carton. Both the vial and carton will be labeled and the kit will be closed with tamper seals so that the site can confirm no interference upon receipt. Keep the vial in the outer carton in order to protect it from light. The number of kits to be shipped to each site for the initial and resupply shipment will be determined between Celgene and IBCSG and will be documented in the drug supply manual.

6.3. Storage and Handling

Nab-Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling nab-Paclitaxel. The use of gloves is recommended. Procedures for proper handling and disposal of anticancer drugs should be followed. Several guidelines on this subject are available (Clinical Oncological Society of Australia, Jones, American Medical Association, American Society of Hospital Pharmacists, Occupational Safety and Health Administration, Jeffrey). There is no general agreement that all of the procedures recommended in these guidelines are necessary or appropriate. However, according to the Active Pharmaceutical Ingredient manufacturer's safety data for paclitaxel, the product should not be released into the environment even though it is a natural, biodegradable product. It is recommended that the material be recovered, if possible, and incinerated under controlled conditions in compliance with the current local and national regulations.

Stability of reconstituted suspension in the vial: From a microbiological point of view, the reconstituted suspension in the vial should be filled into an infusion bag immediately. If not filled immediately, storage times and conditions are the responsibility of the user and should not normally be longer than 8 hours at 2−8°C (36−46°F). If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Stability of the reconstituted suspension in the infusion bag: From a microbiological point of view, the reconstituted suspension in the infusion bag should be used immediately. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user and should not normally be longer than 8 hours at ambient temperature (approximately 25°C [77°F]) and lighting conditions.

6.4. Receipt of the drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

6.5. Unused study drug supplies

Unused study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. The

destruction documents will be shipped to Celgene. If any study drug is lost or damaged, its disposition should be documented in the source documents.

7. Treatments

Patients will be randomized to one of three treatment schedules, which will continue until progressive disease or unacceptable toxicity. Ideally, trial treatment should begin within 5 working days of randomization. A treatment cycle is defined as 28 days.

The Investigator has to change the dose of the chemotherapy if there is an increase or decrease of ≥ 10% in a patient's body weight. The body surface area does not need to be recalculated if the weight change is less than 10%.

7.1. Treatment schedules

7.1.1. Induction nab-Paclitaxel

During the induction phase, all patients initiate treatment with 3 cycles of nab-Paclitaxel:

Arm A: nab-Paclitaxel 125 mg/m^2 days **1, 8, 15** every 28 days
Arm B: nab-Paclitaxel 125 mg/m^2 days **1, 8, 15** every 28 days
Arm C: nab-Paclitaxel 125 mg/m^2 days **1, 8, 15** every 28 days

7.1.2. Maintenance nab-Paclitaxel

During the maintenance phase, patients continue treatment with one of three maintenance schedules until disease progression:

Arm A: nab-Paclitaxel 150 mg/m^2 days **1, 15** every 28 days
Arm B: nab-Paclitaxel 100 mg/m^2 days **1, 8, 15** every 28 days
Arm C: nab-Paclitaxel 75 mg/m^2 days **1, 8, 15, 22** every 28 days

7.1.3. Dosage, administration and schedule

Administer reconstituted nab-Paclitaxel suspension intravenously using an infusion set incorporating a 15 µm filter.

During the induction phase, patients receive for 3 cycles:

Arm A: nab-Paclitaxel 125 mg/m^2 i.v. infusion over 30 minutes, days **1, 8, 15** every 28 days
Arm B: nab-Paclitaxel 125 mg/m^2 i.v. infusion over 30 minutes, days **1, 8, 15** every 28 days
Arm C: nab-Paclitaxel 125 mg/m^2 i.v. infusion over 30 minutes, days **1, 8, 15** every 28 days

In the absence of progressive disease, patients continue to the maintenance phase and receive:

Arm A: nab-Paclitaxel 150 mg/m^2 i.v. infusion over 30 minutes on days **1 and 15** every 28 days
Arm B: nab-Paclitaxel 100 mg/m^2 i.v. infusion over 30 minutes on days **1, 8 and 15** every 28 days
Arm C: nab-Paclitaxel 75 mg/m^2 i.v. infusion over 30 minutes on days **1, 8, 15 and 22** every 28 days

7.2. Dose modifications and delays for toxicity

7.2.1. Hypersensitivity

Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a severe hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel.

7.2.2. Induction phase

In case of toxicities of lower grade or not described below in Table 2, dose reductions following the dose levels in Table 1 may be done according to Investigators' medical judgment.

Table 1 – Dose Levels for Induction Cycles 1 – 3

Dose Level	Induction Days 1, 8, 15
Starting dose	125 mg/m^2
Reduction - 1 dose level	100 mg/m^2

Table 2 – Induction Phase: Cycles 1-3

AE	Grade/count	Required nab-Paclitaxel dose reduction
Platelet count decreased	< 75 x 10^9/L	Hold until improvement to ≥ 100 x10^9/L. Reintroduce at -1 dose level (100 mg/m^2)
Neutrophil count decreased	< 1.5 x10^9/L	Hold until improvement to ≥ 1.5 x10^9/L. Reintroduce at -1 dose level (100 mg/m^2). G-CSF use as a secondary prophylaxis at the discretion of the Investigator
Anemia	Hgb < 9.0g/dL	Hold until improvement to ≥ 9.0 g/dL. Reintroduce at -1 dose level (100 mg/m^2).
Febrile neutropenia	3, 4	Hold until improvement of neutrophils to ≥ 1.5 x10^9/L and no fever. Reintroduce at -1 dose level (100 mg/m^2). G-CSF use as a secondary prophylaxis at the discretion of the Investigators
Peripheral sensory neuropathy	2, 3	Hold until improvement to grade 1 or less. Reintroduce at -1 dose level (100 mg/m^2).
Other toxicities (except specific AEs above)	3, 4	Hold until symptoms improve to grade ≤ 1. Reintroduce at -1 dose level (100 mg/m^2).
Note: Physicians should manage patients according to their medical judgment based on the particular clinical circumstances.		

7.2.3. Maintenance phase: cycles ≥ 4

For patients randomized to arm A: The maintenance phase needs to start at the assigned starting dose (150 mg/m^2 days 1 and 15), regardless of whether the dose in the induction phase was kept at 125 mg/m^2 or had to be reduced to 100 mg/m^2.

In case of toxicities of lower grade or not described below in Table 4, dose reductions following the dose levels in Table 3 may be done according to Investigators' medical judgment.

Table 3 – Dose Levels for Maintenance Cycles ≥4

Dose Level	Maintenance Arm A Days 1, 15	Maintenance Arm B Days 1, 8, 15	Maintenance Arm C Days 1, 8, 15, 22
Starting dose	150 mg/m^2	100 mg/m^2	75 mg/m^2
Reduction - 1 dose level	125 mg/m^2	75 mg/m^2	60 mg/m^2
Reduction - 2 dose levels	100 mg/m^2	Remain at 75 mg/m^2	Remain at 60 mg/m^2

Table 4 – Maintenance Phase: Cycles ≥4

AE	Grade/count	Required nab-Paclitaxel dose reduction
Platelet count decreased	< 75 x 10^9/L	Hold until improvement to ≥ 75 x10^9/L. Reintroduce at next lower dose level.
Neutrophil count decreased	<1.5 x 10^9/L	Hold until improvement to ≥ 1.5 x 10^9/L. Reintroduce at next lower dose level. G-CSF use as a secondary prophylaxis at the discretion of the Investigator
Anemia	Hgb <9.0 g/dL	Hold until improvement to ≥ 9.0 g/dL. Consider reducing to next lower dose level.
Febrile neutropenia	3, 4	Hold until improvement of neutrophils to ≥ 1.5 x 10^9/L and no fever. Reintroduce at the next lower dose level. G-CSF use as a secondary prophylaxis at the discretion of the Investigators.
Peripheral sensory neuropathy	2, 3	Hold until improvement to grade 1 or less. Reintroduce at next lower dose level.
Other toxicities (except specific AEs above)	3, 4	Hold until symptoms improve to grade ≤ 1. Reintroduce at the next lower dose level.
Note: Physicians should manage patients according to their medical judgment based on the particular clinical circumstances.		

7.2.4. Treatment delay or discontinuation

Continuing treatment with nab-paclitaxel for as long as possible is the hypothesis underlying the SNAP protocol. Therefore, dose reductions are preferred, rather than delays or discontinuations. If the treating physician feels it is in the best interest of the patient to discontinue SNAP treatment, contact IBCSG (ibcsg42_SNAP@fstrf.org) before treatment discontinuation to discuss next steps.

7.3. Duration 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:

- Objective disease progression

- Unacceptable adverse event(s)
- Intercurrent illness that prevents further administration of trial treatment
- Patient demonstrates an inability or unwillingness to comply with the treatment regimen and/or study requirements
- Patient declines further trial treatment
- General or specific changes in the patient's condition which render her unacceptable for further treatment in the opinion of the treating Investigator

Patients who discontinue treatment for any reason other than objective disease progression will continue to be followed until documented disease progression on the same schedule, as per Section 10.5 and have an end of treatment visit as per section 10.4.

7.4. 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 other than a decision by the patient to decline any further participation in the study requirements and/or to decline further collection of data (see Section 15.5). If the patient discontinues treatment for any of the reasons listed in the prior subsection, she should continue to be followed according to protocol and eCRFs should be completed as expected as described in Section 11.1.

7.5. Concomitant medication

The following agents may not be taken at any time during trial treatment:

- Chemotherapy, antiangiogenic drugs including bevacizumab
- Investigational anti-cancer treatments

Concomitant medications are any prescription medications or over-the-counter preparations used by the patient from 2 weeks before the start of trial treatment until the completion of trial treatment. All concomitant medications will be recorded in the eCRF (Form 42-CCM) with indication and dates of administration. The following may be administered during trial treatment:

- Continuation of previously started LHRH agonists
- Bisphosphonates
- Denosumab
- Antiemetics
- G-CSF, epoetin
- Steroid prophylaxis

The metabolism of paclitaxel is catalyzed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

8. Safety, adverse events and reporting

8.1. Adverse effects of nab-Paclitaxel

The following adverse reactions have been reported:

Very common (≥ 10%):

Blood and lymphatic system: Neutropenia, anemia, thrombocytopenia, lymphopenia, bone marrow suppression

Metabolism and nutrition system: Anorexia, hypokalemia, dehydration, decreased appetite

Nervous system disorders: Peripheral neuropathy, neuropathy, hypoesthesia, paresthesia, dizziness, dysgeusia, headache

Psychiatric disorders: Insomnia, depression

Respiratory, thoracic and mediastical disorders: Epistaxis, cough, dyspnea.

Gastrointestinal disorders: Nausea, diarrhea, vomiting, constipation, stomatitis, abdominal pain, abdominal pain upper

Skin and subcutaneous tissue disorders: Alopecia, rash, nail disorder, pruritus

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, pain in extremity

General disorders: Fatigue, asthenia, pyrexia, chills

Investigations: Increased alanine aminotransferase, decreased weight

Common (1 – 10%):

Infection: Sepsis, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis, nail infection, oral candidiasis, pneumonia, bronchitis

Blood and lymphatic system: Febrile neutropenia, pancytopenia

Metabolism and nutrition system: decreased appetite

Psychiatric disorders: Anxiety

Nervous system disorders: Ataxia, sensory disturbance, somnolence.

Eye disorders: Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis, visual impairment

Ear and labyrinth disorders: Vertigo

Cardiac disorders: Cardiac failure congestive, tachycardia, palpitations

Vascular disorders: Deep vein thrombosis, hot flushes, hypertension, lymphedema, hypotension

Respiratory, thoracic and mediastinal disorders: Pneumonitis, oropharyngeal pain, pharyngolaryngeal pain, nasal congestion

Gastrointestinal disorders: Colitis, intestinal obstruction, small intestinal obstruction, abdominal distension, dyspepsia, gastroesophageal reflux disease, oral hypesthesia, dry mouth

Hepatobiliary Disorders: Cholangitis, hyperbilirubinaemia

Skin and subcutaneous tissue disorders: dry skin, erythema, nail pigmentation/ discoloration, skin hyperpigmentation, onycholysis, nail changes, erythema, palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders: bone pain, back pain, muscle cramps, limb pain, muscular weakness

Renal and urinary disorders: Acute renal failure, hematuria

General disorders: Peripheral edema, mucosal inflammation, pain, rigors, edema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia, infusion site reaction

Investigations: Increased aspartate aminotransferase, decreased hematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase, increased blood creatinine

Uncommon (0.1 – 1%):

Infection: Nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection

Blood and lymphatic system: Thrombotic thrombocytopenic purpura

Immune system disorders: Hypersensitivity

Metabolism and nutrition system: Hypophosphatemia, fluid retention, hypoalbuminemia, polydipsia, hyperglycemia, hypocalcemia, hypoglycemia, hyponatremia

Psychiatric disorders: Restlessness

Nervous system disorders: VIIth nerve paralysis, polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor, facial palsy

Eye disorders: Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus, keratitis, cystoid macular edema, maculopathy

Ear and labyrinth disorders: Ear pain, tinnitus

Cardiac disorders: Atrioventricular block, hypotension, peripheral coldness, orthostatic hypotension

Respiratory, thoracic and mediastical disorders: Productive cough, exertional dyspnea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing, pulmonary emboli, pulmonary thromboembolism, dry throat

Gastrointestinal disorders: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, esophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal hemorrhage

Skin and subcutaneous tissue disorders: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, neutropenia rash, dermatitis, night sweats, maculo-

papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, skin lesion, swollen face, erythema multiforme

Musculoskeletal and connective tissue disorders: Chest wall pain, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort

Renal and urinary disorders: Hemolytic-uremic syndrome, dysuria, pollakiuria, nocturia, polyuria, urinary incontinence

Reproductive system and breast disorders: Breast pain

General disorders: Chest discomfort, abnormal gait, swelling, injection site reaction

Investigations: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood glucose, increased blood phosphorus, decreased blood potassium

Injury, poisoning and procedural complications: Contusion

Rare (0.01 – 0.1%):

Blood and lymphatic system: Pancytopenia

Immune system disorders: Severe hypersensitivity

Cardiac disorders: Bradycardia, cardiac arrest, left ventricular dysfunction

Vascular disorders: Thrombosis

Respiratory, thoracic and mediastinal disorders: Interstitial pneumonitis

General disorders and administration site conditions: Extravasation

Injury, poisoning and procedural complications: Radiation recall phenomenon, radiation pneumonitis

Very Rare (< 0.01 %):

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis

8.2. 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. The CTCAE is available for downloading on the internet (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). An interactive version can be found at http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx.

An adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after the final dose, regardless of whether it is considered related to a medication.

In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the Investigator assesses as possibly related to the trial treatment should be considered an adverse event.

Symptoms of the targeted cancer (if applicable) should not be reported as adverse events.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

8.2.1. 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 subject. 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 study 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 subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

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

8.2.2. Causality

The Investigator must determine the relationship between the administration of nab-Paclitaxel and the occurrence of an adverse event (AE) or serious adverse event (SAE) as “not suspected” or “suspected” as defined below:

Not suspected:	The temporal relationship of the adverse event to nab-Paclitaxel 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 nab-Paclitaxel administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.3. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

8.2.4. Action taken

The Investigator will report the action taken with nab-Paclitaxel as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of nab-Paclitaxel, as appropriate) and report if concomitant and/or additional treatments were given for the event.

8.3. Targeted adverse events

The presence or absence of the following AEs must be indicated on each required AE form (Form 42-AE):

- Peripheral sensory neuropathy
- Neutrophil count decreased
- Febrile neutropenia
- Anemia
- Platelet count decreased
- Nausea
- Vomiting
- Diarrhea
- Cardiac disorders:
  - Ventricular arrhythmia
  - Sinus tachycardia
  - Heart failure
  - Left ventricular systolic dysfunction
- Recurrent laryngeal nerve palsies
- Allergic reaction
- Blood antidiuretic hormone abnormal
- Pneumonitis

8.4. Rare AEs to be reported

The following AEs have been very rarely observed; their occurrence should be reported on the adverse event form (Form 42-AE) under “other, specify”:

- Vocal cord paresis
- Macular edema
- Blindness, uni- or bilateral

8.5. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if any of the following apply:

- Results in discontinuation from the study
- Requires treatment, modification/ interruption of nab-Paclitaxel dose, or any other therapeutic intervention
- Is judged to be of significant clinical importance

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE, if it is a targeted AE or another AE grade 3 or higher.

8.6. Serious adverse event (SAE) reporting

8.6.1. Definition

An SAE is defined in general as any undesirable medical occurrence/adverse drug experience that occurs during or within 30 days after stopping 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
- Congenital anomaly or birth defect
- Secondary (non-breast) malignancy
- Constitutes an “important medical event”:

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.

All SAEs must also be reported for the period in which the trial protocol interferes with the standard medical treatment given to the patient. After completion of trial treatments, report all SAEs that are considered at least possibly related to previous trial treatment. Second (non-breast) malignancies and congenital anomalies should be regarded as SAEs, regardless of whether they occur during or after study treatment. These events should be reported on the SAE eCRFs (42-SAE-A and 42-SAE-B).

SAE also includes any other event that the Investigator or the IBCSG Safety Office judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred.

An unexpected adverse event is one that is not listed as a known toxicity of the investigational drug in the summary of product characteristics.

A related adverse event is one for which the Investigator assesses that there is a reasonable possibility that the event is related to the investigational drug. All adverse events judged as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

8.6.2. Exceptions to the definition

Hospitalizations occurring under the following circumstances are not considered to be SAEs:

- Elective surgery
- Occur on an outpatient basis and do not result in admission (hospitalization < 24 h)
- 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 42-TEV and not as an SAE.

8.6.3. Reporting SAEs

Any SAE occurring in a patient after providing informed consent must be reported. Information about all SAEs will be collected and recorded on the IBCSG Serious Adverse Event eCRFs (42-SAE-A and 42-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 via iDataFax. A copy is automatically forwarded to the IBCSG Safety Office for medical review.
- Follow-up information should be completed, via iDataFax, on the Serious Adverse Event (SAE-B) eCRF 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 subject'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 these examinations were performed should be sent by fax into the DataFax system. Care should be taken to ensure that the patient's identity is protected and the patient's Randomization ID Number is properly included on ALL pages of any reports. For laboratory results, include the laboratory normal ranges.
- In the event the eCRF system is not working, the SAE Forms can be sent via fax into the DataFax system.

If the original SAE (42-SAE-A and 42-SAE-B) was submitted by fax, the original forms and the fax confirmation sheet(s) must be kept at the Participating Center.

The IBCSG will inform Celgene and other appropriate persons about all SAEs within 24 hours of receipt at the IBCSG Safety Office.

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 website (www.ibcsg.org).

8.7. Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a patient occurring during trial treatment, or within 30 days of the last dose of nab-Paclitaxel, should be reported within 24 hours of having knowledge of the event. Nab-Paclitaxel is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported, using the pregnancy eCRF (42-PREG), to the IBCSG who will inform Celgene immediately.

The patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy, and must notify IBCSG immediately about the outcome of the pregnancy by completing the corresponding section on the pregnancy form (42-PREG).

All neonatal deaths that occur within 28 days of birth should be reported as SAEs, without regard to causality. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to nab-Paclitaxel should also be reported within 24 hours of the Investigator's knowledge of the event using the eCRFs (42-SAE-A and 42-SAE-B).

8.8. Safety review of nab-Paclitaxel

Every six months, the reported AEs will be summarized in a safety report, according to randomized treatment assignment; separate tabulations will include those events reported during the first 3 cycles of induction therapy, those AEs reported during subsequent maintenance cycles, and those reported at any time. Investigators should document treatment and AEs immediately at the end of each cycle by completing the appropriate eCRFs.

The safety reports will be reviewed by the Data and Safety Monitoring Committee (see section 12.5).

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

9.1. Introduction

All randomized patients will be evaluated for disease response and progression according to the revised Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) (30). In this trial, patients may have **measurable or non-measurable** disease (see definitions below). Patients will be re-evaluated every 12 weeks.

9.2. 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 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 ≤ 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 ≥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.

9.3. Measurability of tumor at baseline

9.3.1 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.

9.3.2 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

9.4. Selection of target lesions

For patients with measurable disease, target lesions should be identified, measured and recorded at baseline (Form 42-TEV-B). 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 reported 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.

9.5. Selection of non-target lesions

For patients with measurable or non-measurable disease, non-target lesions should be identified. For patients with measurable disease, all other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

For patients with non-measurable disease, non-target lesions or sites of disease must be identified and recorded at baseline (Form 42-TEV-B). These non-target sites will be followed for tumor evaluation (Form 42-TEV).

For non-target lesions, measurements are not required, but the presence or absence of each should be noted throughout follow-up (Form 42-TEV). It is possible to record multiple non-target lesions as a single item on the eCRF (e.g., "multiple liver metastases").

9.6. 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 study. 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 9.8) 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 study.

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.

9.7. Evaluation of non-target lesions (measurable or non-measurable disease)

- 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.

9.8. 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 scans confirm 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.

9.9. 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.

9.10. 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 the table below.

9.10.1. For patients with measurable disease

Table 5 – 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.			

9.10.2. For patients with non-measurable disease only

Table 6 – 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.		

9.11. Determination of best overall response and response duration

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial. Best overall response will be determined by a team consisting of the study chair, co-chair and IBCSG Head of Medical Affairs.

Among patients with measurable disease, the **duration of response** is defined as the time from which the criteria for partial or complete response are first met until disease progression. Among patients with non-measurable disease, the duration of response is defined as the time from which the criteria for CR are first met until disease progression.

9.12. Progression-free survival

Progression-free survival (PFS) is defined as time from randomization until objective disease progression or death, whichever occurs first.

Patients with new non-breast cancer malignancy must continue to be followed for progression of the original breast cancer. For patients without progression, follow-up will be censored at the date of last disease assessment without progression, unless death occurs within a short period of time (12 weeks) 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 7.4), including those who initiate non-protocol therapy prior to progression, will be followed for disease progression.

10. Clinical and laboratory evaluations

10.1. Prior to randomization

Table 7 – Evaluations Prior to Randomization

Investigation	Timing
Patient informed consent	Prior to randomization
Medical history (including height) & physical exam	Within 14 days prior to randomization
ECOG performance status and life expectancy	Within 14 days prior to randomization
Vital signs (Blood pressure and pulse rate after 5 minutes in sitting position; body temperature; body weight; respiratory rate)	Within 14 days prior to randomization
MUGA or echocardiogram	Within 14 days prior to randomization. If the patient is clinically cardiac compensated with no heart symptoms, these can be done up to 6 months prior to randomization
Hematology (ANC, hemoglobin, platelets)	Within 14 days prior to randomization
Biochemistry (ALT (SGPT), AST (SGOT), total bilirubin, serum creatinine or calculated creatinine clearance acc. Cockcroft and Gault)	Within 14 days prior to randomization
Concomitant medications	Medications used within 14 days prior to randomization
Pregnancy test (for patients with child-bearing potential)	Within 14 days prior to randomization; Must be repeated if time from pregnancy test today 1 of cycle 1 exceeds 14 days.
Verify all inclusion/exclusion criteria	Prior to randomization
Baseline symptoms	Observed within 14 days prior to treatment
QL self-assessment	Within 28 days prior to randomization, after patient informed consent
Tumor evaluation (RECIST 1.1)	Within 28 days prior to randomization, after patient informed consent
HER2 analysis	Prior to randomization
ER and PgR status	Prior to randomization
Menopausal status	Prior to randomization
FFPE tumor tissue sample from primary tumor (breast lesion) and if available from metastatic biopsy	Prior to randomization

10.2. During induction nab-Paclitaxel

Table 8 – Evaluations During Induction

Investigation	Prior to treatment, each of 3 cycles		
	Day 1	Day 8	Day 15
Physical exam	X		
Vital signs	X		
MUGA or echocardiogram only if clinically indicated	X		
Hematology	X	X	X
Biochemistry	X		
Concomitant medications	Continuously as started or re-started		
Performance status	X		
QL self-assessment If baseline QL was within 14 days prior to treatment start, no QL form has to be completed at day 1 of cycle 1	X		
AEs	At the end of each cycle		
Tumor evaluation (RECIST 1.1)	12 weeks from day of randomization. If evaluation shows progression, stop trial treatment.		

10.3. During maintenance nab-Paclitaxel

Table 9 – Evaluations During Maintenance

Investigation	Prior to treatment, each cycle			
	Day 1	Day 8 (Arms B&C) only	Day 15	Day 22 (Arm C only)
Physical exam	X			
Vital signs	X			
MUGA or echocardiogram only if clinically indicated	X			
Hematology	X	X	X	X
Biochemistry	X			
Concomitant medications	continuously			
Performance status	X			
QL self-assessment	X			
AEs	X	At the end of each cycle		
Tumor evaluation (RECIST 1.1)	Every 12 weeks. If evaluation shows progression, stop trial treatment			

10.4. After discontinuation of trial treatment

Table 10 – Evaluations After Discontinuation

Investigation	
End of treatment visit within 30 days after stop of trial treatment	• Record last dose of trial treatment and document reason for stopping treatment • Physical exam, vital signs, performance status • Hematology, blood chemistry • Adverse events and concomitant medications up to 30 days after last dose of trial treatment • Quality of life self-assessment form
Tumor evaluation (RECIST 1.1)	If progression is not documented at last routine tumor evaluation then tumor evaluation must be continued on the same schedule (every 12 weeks +/- 2 weeks) until progression is documented.
Post-treatment follow-up	Patients will be followed for survival status. Follow up continues until end of trial (approx. 18 months after randomization of the last patient; see Section 3.2)

Notes for Sections 10.1-10.4

(a) Adverse events (AE) should be graded using the NCI CTCAE version 4 (Appendix II). Targeted adverse events occurring during and up to 30 days after discontinuation of trial treatment should be recorded on the eCRF (42-AE).

(b) Quality of Life (QL) self-assessment forms should be completed on day 1 of each of the first 12 cycles, prior to any diagnostic procedures (or communication of diagnostic information) or receiving chemotherapy. If baseline QL was within 14 days prior to treatment start, no QL form has to be completed at day 1 of cycle 1. QL forms must be completed and submitted according to guidelines in Section 14. Because they are completed by the patient, QL Forms cannot be completed in iDataFax and must instead be faxed into the DataFax System.

(c) Tumor evaluation: CT/MRI scans of the chest, abdomen and pelvis must be available at screening (i.e., within the 28 days between signing the informed consent form and

randomization of the patient) and will be performed every 12 weeks from the day of randomization until documented disease progression.

Bone scans should be performed at baseline in patients with known bone metastases and where there is clinical suspicion of previously unknown bone metastasis. Bone scan (if clinically indicated) are acceptable ≤ 8 weeks before randomization. In case of a positive bone scan, correlative conventional imaging as defined by RECIST 1.1 of the respective lesion(s) should be performed. These areas should have repeat conventional imaging at every scheduled imaging time point. Subsequent imaging with bone scans after baseline should be based on clinical indication, at the discretion of the Investigator. For example, when complete response is identified in target disease or when progression in bone is suspected (to confirm the presence or disappearance of bone lesions).

(d) Section 11 (Data Submission) provides details on eCRF schedule and submission.

10.5. Follow-up

Patients should be followed through the end of the trial (approximately 18 months after the last patient is randomized) or death, whichever occurs first. Patients who discontinue treatment with documented disease progression will be followed for survival status. Patients who discontinue treatment without disease progression will be followed with continued tumor evaluations on the same schedule (every 12 weeks +/- 2 weeks) until progression is documented. Other treatments prior to progression should be reported; after progression patients will be followed for survival status only.

11. 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 study. Timeliness of data submission and quality of data will result in fewer queries to the Center.

Case Report Forms should be completed electronically (eCRF) in iDataFax (with the exception of QL self-assessment Forms, Pathology Reports, SAE related reports and possibly laboratory reports, which must be faxed to the DataFax system) by either the Principal Investigator or designee, according to the Authorization Log. The following eCRFs/data are to be submitted at the indicated times by the Participating Centers for each patient.

11.1. Case report forms schedule

Forms	*Description/Name*	*Forms Submission*
Registration/Randomization		***ALL data should be submitted in iDataFax (iDF) (unless otherwise specified)***
Informed Consent Form	Consent to participation in clinical trial	Obtain before randomization and keep with patient records as documentation (hard copy only).
42-A	Confirmation of Registration Form	Complete in iDF after you or your Randomization Center has randomized the patient in the IBCSG Registration/Randomization System.
42-QLC	Quality of Life	Complete prior to randomization and submit to DataFax via fax or DFSend.
Baseline		
42-H	History Form	Complete in iDF within 1 week of randomization.
Path. report	Pathology Report	Submit Report to DataFax, via fax or DFSend, within 1 week of randomization.
42-BS	Baseline Symptoms Form	Complete in iDF within 1 week of randomization.
42-CCM	Concomitant Medications Form	Complete in iDF each time a medication is started, amended, or ended, including medications taken within 14 days prior to start of treatment.
42-TEV-B	Baseline Tumor Evaluation Form	Complete in iDF within 1 week of randomization.
During trial treatment		
42-AE	Adverse Events Form	Complete in iDF at the end of each cycle of chemotherapy = day 1 of next cycle.
42-TEV	Tumor Evaluation Form	Complete in iDF after every tumor evaluation (every 12 weeks).
42-CCM	Concomitant Medications Form	Review the original CCM Form at the end of each cycle. Update in iDF any current medications if needed and add new medications taken.
42-QLC	Quality of Life (self-assessment) Form	Submit to DataFax, via fax or DFSend, after completion, day 1 of each of the first 12 cycles. If baseline QL was within 14 days prior to day 1 of cycle 1, no QL form has to be completed at day 1 of cycle 1.
42-CT	Chemotherapy Form (including lab values)	Complete in iDF at the end of each cycle.
Follow Up (after discontinuation of trial treatment)		
42-TC	Treatment Completion Form	Complete in iDF within 30 days of trial treatment stop.
42-QLC	Quality of Life self-assessment form	Submit to DataFax, via fax or DFSend, after completion at end-of-treatment visit.
42-E	Follow up Form	Complete in iDF every 3 months after trial treatment is discontinued.
42-TEV	Tumor Evaluation Form	Complete in iDF at end of treatment and every 12 weeks until progression, *only if* patient discontinued trial treatment prior to documented progression.
42-AE	Adverse Events Form	Complete in iDF 30 days after the last dose of trial treatment.
Event Driven		
42-SAE-A	Serious Adverse Event initial report	Complete within 24 hours of the SAE in iDF. If iDF is not available, fax the form within 24 hours to DataFax.
42-SAE-B	Serious Adverse Event B follow-up report	Complete in iDF within 15 days of completion of initial report (42-SAE-A). If event is not resolved in 15 days, complete 42-SAE-B again at the time of resolution.
42-PREG	Pregnancy Form	Complete in iDF if a patient becomes pregnant on trial treatment. Complete the second section of the form at the end of pregnancy.
42-COC	Change of Consent Form	Complete in iDF if there is any change in patient's consent to participate in the trial, see Section 15.5.2.
42-E-Death	Death Form	Complete in iDF if a patient dies.

If at the end of the trial a patient has not progressed and wants to continue nab-Paclitaxel, the drug will be provided until progressive disease. In this case, adverse events, serious adverse events, treatment, and concomitant medications will continue to be collected.

The Data Managers' Manual for this trial contains instructions for completing forms. Please note that we expect forms submission, unless the patient has explicitly declined any further participation in the study requirements and/or explicitly declined further collection of data. For instructions on forms submission in these cases, please contact the IBCSG Data Management Center at ibcsg42_SNAP@fstrf.org .

11.2. Signing and submitting forms

All forms should be signed by the Principal Investigator or designee. An Authorization Log should be completed at each Participating Center. Instructions for completing the Authorization Log can be found in the Authorization Log Manual, available on the IBCSG website (www.ibcsg.org).

CRFs, including SAE Forms, should be completed electronically in iDataFax. Reports (lab, pathology, etc.) and any other non-eCRF data (such as QL forms) must be faxed into the DataFax system. Any patient identification on such reports (name, date of birth, hospital number) should be carefully blacked out and every page identified by the Patient Identification Number (ID) assigned by the IBCSG Registration/ Randomization System. Full instructions on submitting forms will be distributed to each Participating Center and are available on the IBCSG website (www.ibcsg.org). Also available on the website is the "Data Fax toll free numbers" document.

For Centers participating through a Group: Please consult your Participating Group Specific Logistical Information for special instructions about how to submit data.

11.3. 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 Quality Control (QC) Reports, which contain queries and forms requests. The IBCSG Coordinating Center in Bern, Switzerland will provide medical review and summaries of SAEs. The IBCSG Statistical Center in Boston, MA USA will perform the data analysis.

11.4. Investigator's file

Each Participating Center should keep documentation about this trial in an Investigator's File, which should include all of the following documents (ICH GCP essential documents):

- Protocol activation/distribution letter
- Protocol and appendices
- Amendments
- Signed Protocol Signature Pages
- Sample CRFs including blank SAE Forms
- Data Managers' Manual
- Obvious Corrections Documents and Signature Pages
- Randomization Manual
- Instructions for Using the DataFax System

- iDataFax User Manual
- Drug Supply Manual
- Participating Group/Country Specific Logistical Information
- Patient information and Informed Consent templates approved by Ethics Committee
- Investigator's Brochure and updates
- Ethics Committee approval of protocol, Patient Information Sheet and IC, amendments
- Ethics Committee review of SAE, Investigators' alert, and other documents
- Correspondence with Ethics Committee
- Agreement with IBCSG
- Clinical trial insurance policy
- Center Activation e-mail from the Data Management Center
- Correspondence with IBCSG
- SAE reports from IBCSG
- Accrual reports from IBCSG
- Normal laboratory values/reference ranges
- Laboratory Certifications
- CV of Principal Investigator and Co-Investigators (including GCP training certificate)
- Authorization Log (see below)
- Patient identification log (see below)
- Drug accountability log (including certificates of destruction if applicable)
- ICH GCP guidelines/Declaration of Helsinki and updates
- Audit certificates
- IBCSG Training certificates
- Monitoring reports
- IBCSG and/or trial newsletters
- Other Reports from IBCSG (Biostatistician Report, Data Safety Monitoring Committee minutes, Annual Safety Reports, IBCSG EC Approval)

11.5. Authorization log

The Principal Investigator should identify the other members of the Clinical Trial Team who are supervised by the Principal Investigator and approved to provide information in CRFs, queries, etc. A manual for completing the Authorization Log is available on the IBCSG website.

11.6. Patient identification log

As per GCP, patients have the right to confidentiality. Therefore, no patients' names should be used in CRFs or any other documentation transmitted to IBCSG central offices. The only item that is used to identify a patient is the Patient ID (randomization number assigned by the Randomization System). It is therefore imperative that the local Data Manager keeps an identification log for all patients entered in this trial including:

- Patient's name
- Patient ID (randomization number)
- Date of birth

Other items that could be included are treatment assignment and date of randomization.

12. Statistical considerations

The primary objective of this randomized phase II trial is to evaluate the efficacy of three different schedules of nab-Paclitaxel administration. Efficacy is measured by progression-free survival (PFS), using a historical reference of PFS of docetaxel for first-line treatment of metastatic breast cancer (28), assumed as median of 7 months. A total of 258 patients will be stratified as described in section 5.4 and randomized in a 1:1:1 allocation, which will result in approximately 86 patients in each arm.

In the original design of this phase II trial, patients will receive three cycles of nab-Paclitaxel 150 mg/m^2 days 1, 8, 15 every 28 days during induction phase. Following the first safety review of 48 treated patients, it was decided to modify the dose in the induction phase to 125 mg/m².

12.1. Primary endpoint

The primary efficacy endpoint of PFS will be evaluated among three treatment arms. The definition of PFS is given in Section 9.12. For each arm separately, in three independent tests, PFS will be compared to the historic PFS of first-line docetaxel. For each of the tests, the type I error will be controlled at one-sided 0.05.

12.1.1. Sample size justification

Assuming the median PFS of docetaxel is 7 months and the median PFS of a nab-Paclitaxel treatment schedule is 10 months, with 76 patients in an arm, and an accrual rate of 8 patients per month for an accrual period of 30 months plus an additional 12 months of follow up to reach the target number of events, the study will have 88% power to detect an improvement in PFS in a nab-Paclitaxel treatment schedule relative to docetaxel, using a one-sample log-rank test at a one-sided significance level of 0.05. The target number of events per arm is 63. Assuming a 12% drop out rate and those patients do not contribute events, the sample size is increased to 86 patients per arm. Exponential failures were assumed for the sample size calculations (31), which were carried out using a locally-maintained library in R (R Foundation for Statistical Computing, Vienna, Austria).

A higher than expected drop out rate was observed during trial conduct, and based on recommendations from the IBCSG DSMC the sample size was increased. As of November 2014, 9 drop outs who will not contribute events had been documented. Considering the subset of patients enrolled prior to April 2014 who had longer follow-up, the drop out rate was 9.2% (8 of 87 patients). Thus as longer follow-up accumulates, the drop out rate was anticipated to rise to as much as 12%. To obtain the originally planned power, the accrual per arm was increased to 86 patients (76/0.88 = 86.4).

To reach the target number of events, the design assumed accrual duration of 30 months and 12 months of additional follow-up. As of the fourth quarter of 2014, an accrual duration of 24 to 26 months is anticipated. An additional follow up of 16 to 18 months, resulting in the same anticipated maximum follow up of 42 months and end of trial approximately 4 years after randomization of the first patient, will reach the target number of events.

12.1.2. Analysis of the primary endpoint

Randomized patients who received at least one dose of the trial treatment will be included in the PFS analysis. For each arm separately, PFS will be compared to the historic PFS of first-line docetaxel using a one-sample log-rank test. PFS distributions will be summarized using the method of Kaplan-Meier and the two-sided 90% confidence interval (CI) for the median PFS will be provided.

For each arm, PFS distribution will also be summarized separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

Subgroup analyses according to age groups and ER status as defined for the stratification will be performed as exploratory analyses.

12.2. Secondary objectives

12.2.1. Tolerability

Tolerability will be evaluated in each of the three treatment arms separately. The frequencies of adverse events (AE) while on treatment will be summarized and tabulated by arm; separate tabulations will include those AEs reported during the induction phase, those events reported during the maintenance phase, and those reported at any time. These tabulations will also be done separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2). Randomized patients who received at least one dose of the trial treatment will be included in the tolerability analyses. Two frequently-observed AEs in patients receiving nab-Paclitaxel were neutropenia and sensory neuropathy (28). The two-sided 90% CIs of grade 3-4 neutropenia and grade ≥ 2 sensory neuropathy will be provided by arm. With 86 patients in each arm, the width of the two-sided exact binomial 90% CI for the rate of grade 3-4 neutropenia (or grade ≥ 2 sensory neuropathy) will be no wider than 19%, as summarized in Table 11.

Table 11 shows the width of a two-sided exact binomial 90% CI for a range of possible true AE rates, for a sample size of 86 patients in a treatment arm.

Table 11 – Confidence Intervals (CI) for AE Rates (%)

True AE rate (%)	5%	10%	20%	30%	40%	50%
90% CI width	8.7	11.4	15.1	17.1	18.3	18.9

For each arm, the two-sided 90% CIs of grade 3-4 neutropenia and grade ≥ 2 peripheral sensory neuropathy will also be provided separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

12.2.2. Feasibility

Feasibility will be evaluated in each of the three treatment arms separately. Feasibility is defined as the percentage of patients who complete treatment according to the protocol for at least 24 weeks. Randomized patients who received at least one dose of the trial treatment will be included in the analysis. The percentages will be summarized by arm with two-sided 90% CI. In each arm, the width of the two-sided exact binomial 90% CI will be no wider than 19% (similarly as in Table 11). The percentages of the feasibility will also be summarized for each arm separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2). In addition, the cumulative amount of nab-Paclitaxel administered and the total duration of therapy will all be summarized; dose modifications, dose

interruptions, reason for treatment discontinuation will also be summarized by treatment arm and different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

12.2.3. Disease Response

The primary measure is the Disease Control Rate (DCR). The definition of disease control is given in section 2.4. Randomized patients who received at least one dose of the trial treatment will be included in the analysis. The DCR and two-sided 90% CI of DCR will be assessed for each arm separately.

Additional measures that will be characterized similarly are the best overall response (defined in section 9.11) and the overall response at the first restaging after the 3 cycles of induction therapy (as defined in section 9.10).

Among the patients who experience a CR or PR, the distribution of duration of response (as defined in section 9.11) will be summarized using the method of Kaplan-Meier for each arm separately. The timing at which response is achieved (i.e., of the start of the duration of response interval) will be summarized descriptively.

DCR, best overall response, the overall response after the 3 cycles of induction therapy, and duration of response will also be summarized for each arm separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

12.2.4. Overall Survival (OS)

The definition of OS is given in section 2.4. Randomized patients who received at least one dose of the trial treatment will be included in the analysis. OS distributions will be summarized using the method of Kaplan-Meier and the two-sided 90% CI for the median OS will be provided for each treatment arm separately, and also be summarized for each arm separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

12.2.5. Quality of Life (QL)

The QL study is described in Section 14.

12.2.6. Translational Research

The translational research studies are described in Section 13.4.

12.3. Interim analyses

No interim efficacy analyses are planned. Accrual, accumulation of PFS events and adverse events will be monitored throughout the trial and presented to the IBCSG Data and Safety Monitoring Committee (DSMC) approximately every six months.

We prospectively plan two focused safety reviews of dose-reductions and treatment discontinuations because of toxicity (as described in Section 7.3) during the induction phase with nab-Paclitaxel 150 mg/m^2 days 1,8,15 every 28 days for 3 cycles. The reviews will be done without regard to randomized treatment assignment because the induction phase is the same in each of the three treatment arms. If too few patients are able to complete the induction phase without dose reduction or treatment discontinuation because of toxicity (“complete”), then a modification of the induction phase treatment schedule will be considered.

The guidelines for decision-making are based on the principles of a two-stage design. Fewer than 80% of patients able to "complete" the induction phase is considered as too low, and at least 90% of patients able to "complete" the induction phase is considered as high enough. After treating 48 patients, 39 or fewer patients who "complete" would suggest that a change be considered, whereas greater than 39 patients who "complete" would suggest no change to the induction phase. Assuming the trial continues without change, after treating 120 patients, 101 patients is the critical value for decision-making at the second review. With these guidelines, if "completion" of the induction phase truly is too low, then there is an 0.081 probability of concluding that "completion" is not too low (target α=0.10). If "completion" is truly high enough, then there is a 0.064 probability of concluding that "completion" is not high enough (target β=0.10). If "completion" of the induction phase truly is too low, then there is a 0.649 probability of this conclusion and considering a change.

The population for each of the safety reviews will be the first 48 (20%) and 120 (50%) consecutively randomized patients, after excluding any patient who never starts or discontinues treatment during the induction phase for a reason that is unrelated to toxicity (e.g., objective disease progression); any such patient will be documented as part of the review.

Following the first safety review of 48 treated patients, it was decided to modify the dose in the induction phase to 125 mg/m^2. The second focused safety review as described above will not occur since it would come too late to have an impact on patients' induction treatment. Summary of dose reduction and treatment discontinuation will continue to be part of regular monitoring throughout the trial that is presented to the IBCSG DSMC approximately every six months.

12.4. Accrual

The overall accrual goal of this study is 258 patients. We originally anticipated that the accrual rate will be approximately 8 patients per month and the accrual will be completed within 30 months. As of the fourth quarter of 2014, an accrual duration of 24 to 26 months is anticipated.

12.5. Data and Safety Monitoring Committee (DSMC)

The study will be presented for review to the IBCSG DSMC at each of their semi-annual meetings. Accrual, safety and accumulation of PFS events will be monitored.

13. Pathology and Translational Research

13.1. Central pathology assessment

One formalin fixed, paraffin-embedded (FFPE) block of the primary tumor, representative of the invasive component of the tumor (possibly including at least 5 mm invasive tumor and a minor component of non-neoplastic breast tissue) must be submitted to the IBCSG Central Pathology Office in Milan, Italy. If a metastatic site was biopsied, an additional tumor block from the metastatic site should also be submitted.

Central Pathology Review will be done on all the primary tumors and the metastatic biopsies, and will include histopathological parameters (tumor histology and grade,

occurrence of peritumoral vascular invasion), hormone receptors (estrogen and progesterone receptors), HER2 status, and proliferation (Ki-67 immunostaining).

Central pathology review reports will be available to institution pathologists who wish to see them.

13.2. Submitting biological material to IBCSG

The following items are required for all randomized patients:

1. One FFPE block of tumor from the primary tumor (breast lesion). This should include at least 5mm invasive tumor, and a minor component of normal breast tissue (whenever it is available). Availability of such a block is an eligibility criterion.

And, if a metastatic site has been biopsied,

2. One FFPE block from the diagnostic biopsy of the metastatic site

All pathology reports, and FFPE blocks must be marked with the IBCSG patient ID number. Refer to the IBCSG website for additional FFPE specimen shipping recommendations, and to download the Pro Forma Invoice and IATA certification ("iata650") templates that should be completed for international tissue shipments.

Mailing address for the FFPE blocks and H&E slides:
IBCSG Central Pathology Office
European Institute of Oncology, EIO
Division of Pathology
Via Ripamonti 435
20141 Milano, Italy

E-mail: pathology.ibcsg@ieo.it

13.3. Banking biological material

IBCSG wants to be ready with a suitable tissue bank for assessing the prognostic role of putative marker (SPARC and caveolin) and also for unveiling new markers in the very near future. All FFPE blocks will be banked in the IBCSG Tissue Bank, to have available for Translational Research. If the return of the block is requested, cores (2-4 cores, 1mm thick) for tissue microarray (TMA) construction and cores (2-3 cores, 1mm thick) for banking for future translational research will be taken. DNA will be extracted.

All biological material will be logged in the IBCSG Pathology Material Tracking System /Translational Research System and banked in the IBCSG Tissue Bank.

The use of the biological material for unspecified future research will be under the auspices of the IBCSG Biological Protocols Working Group and any project has to be approved by the IBCSG Ethics Committee. As part of the informed consent process, patients are asked to indicate whether they agree to donate their sample for unspecified future research. The patient's decision is recorded on the IBCSG Confirmation of Registration (A) Form.

13.4. Translational research

Based on preliminary results in pancreatic cancer and in breast cancer, we will investigate the prognostic role of SPARC and caveolin in the whole series of patients, and on both the primary tumor blocks and metastatic biopsies. Immunohistochemistry (IHC) for SPARC

requires staining of the samples both with a monoclonal antibody and a polyclonal antibody. Caveolin will require a single IHC assay with a monoclonal antibody. These assays are added to the evaluation of the primary tumors to ascertain the actual prevalence of their expression in breast cancer. IBCSG wants to assess any change in the expression of these markers between the primary and the metastatic sites, and therefore will re-stain all the metastatic samples to compare the results with the corresponding primaries (32,33).

The IBCSG Central Pathology Office will be responsible for cutting and staining the sections, evaluation by a board-certified pathologist, quality control of at least 10% of the cases by a second board-certified pathologist, adjudication of the equivocal cases; data entry, data quality control by a data manager, banking of the slides and paraffin blocks.

The expression of SPARC and caveolin will be compared between the primary and metastatic sites using Wilcoxon signed rank test. Assuming 90 (35% of 258) patients will have both primary and metastatic samples available, there will be 82% power to detect an effect size of 0.31 with a two-sided significance level 0.05. The effect size is defined as the difference in the expression of SPARC (or caveolin) between the primary and metastatic sites divided by the standard deviation of the difference.

For the primary sites and metastatic sites separately, we will examine whether SPARC and caveolin are prognostic indicators for women with metastatic breast cancer. Patients will be classified by the average z-score algorithm into high-SPARC (average z-score ≥ 0) and low-SPARC group (average z-score < 0) (32). We will compare PFS between the high-SPARC patients and low-SPARC patients. It is suspected that patients with high-SPARC have better PFS (32). Assume 50% of patients will have SPARC status evaluated and 50% of them are high-SPARC. Using two-sided log-rank test and Schoenfeld's approximation, with all the treatment arms combined and with 95 events at the end of the study, we will have 80% power to detect 1.78 hazard ratio for low-SPARC / high-SPARC in PFS at a two-sided significance level of 0.05. The table below shows the hazard ratio for low-SPARC / high-SPARC to be detected with at least 80% power based on various percentages of patients who will have SPARC analyzed.

Table 12 – Detectable Hazard Ratio SPARC Analysis

% of patients have SPARC analyzed	40% (n=103)	45% (n=116)	50% (n=129)
Hazard ratio (low-SPARC / high-SPARC) to be detected with enough power	1.91	1.84	1.78

For caveolin, the expression will be scored as (++), (+), or (-) according to the proportion of positively stained tumor cells (T) and stromal cells (S). The PFS of combined T(++)/S(-) status will be compared to others. It is suspected that T(++)/S(-) will be significantly correlated with unfavorable outcome (33). Assume 50% of patients will have caveolin status evaluated and 5% of them are T(++)/S(-). Using two-sided log-rank test and Schoenfeld's approximation, with all the treatment arms combined and with 95 events at the end of the study, we will have 80% power to detect 3.8 hazard ratio for [T(++)/S(-)] /others in PFS at two-sided significance level of 0.05. The table below shows the hazard ratio for [T(++)/S(-)]/others to be detected with at least 80% power based on various percentages of patients who will have caveolin analyzed.

Table 13 – Detectable Hazard Ratio Caveolin Analysis

% of patients have caveolin analyzed	40% (n=103)	45% (n=116)	50% (n=129)
Hazard ratio [T(++)/S(-)]/ others could be detected with enough power	4.4	4.0	3.8

PFS distributions will be summarized using the method of Kaplan-Meier. Cox regression analysis, adjusted by treatment effect, will be used to assess whether SPARC or caveolin is an independent predictor for PFS.

14. Quality of Life

14.1. Introduction

In patients with HER-2 negative metastatic (stage IV) breast cancer, balancing the trade-offs between treatment efficacy and side-effects is a key issue. Quality of life (QL) is an important outcome in this population, given the limited survival time. Endpoints evaluating the net benefit between efficacy and side-effects have commonly been defined as "clinical benefit" and have not included QL measures. Recently, these endpoints have been referred to as "disease control." The common definition of disease control in patients with metastatic breast cancer is defined as complete (CR) or partial (PR) response, or stable disease (SD) for at least 6 months.

Whether this endpoint could be used as a surrogate measure for patients' perception of treatment effects in clinical trials is an important question. In an earlier trial, patients receiving second-line endocrine treatment for metastatic breast cancer differed in the perception of their QL from the established disease control endpoint (34). Although the groups with CR or PR, and those with SD for at least 6 months had similar times to treatment failure, patients with CR or PR reported substantially better QL, suggesting more beneficial response to the investigated treatments. This finding has not been replicated.

14.2. Objectives

The primary quality of life objective is to explore the change in QL over time until treatment discontinuation for patients on each treatment arm.

Secondary objectives are:

- To compare the change in physical well-being from baseline to 6 months (24 weeks) between treatment arms
- To examine QL in patients with CR/PR as compared to QL in patients who have had SD for at least 6 months (or non-CR/non-PD in the case of non-measurable disease)
- To examine the association between the QL scores at baseline and treatment feasibility

QL endpoints include: physical well-being (primary endpoint), mood, coping effort, overall treatment burden, appetite, tiredness, hair loss and feeling sick (nausea/vomiting) as measured by linear analog self-assessment (LASA) indicators; sensory neuropathy as

measured by 4-item subscale of FACT/GOG-Ntx. Treatment feasibility is defined in Section 2.4.

14.3. Patient selection

All patients randomized into IBCSG Trial 42-12 must complete QL questionnaires. There should be no patient selection within Participating Centers. Completion of the baseline 42-QLC questionnaire is mandatory prior to randomization, and is thus considered an eligibility criterion in Section 4.1.

14.4. QL design

A monthly longitudinal assessment is used to assess differential effects of the randomized treatments on patients' QL. Patients are asked to complete a QL questionnaire:

- At baseline (prior to randomization)
- At day 1 of every cycle for the first 12 cycles on trial treatment, or until treatment discontinuation, whichever occurs first. If baseline QL was within 14 days prior to treatment start, no QL form has to be completed at day 1 of cycle 1. It is important that the QL questionnaire is completed before any procedures or treatment, as described in Section 14.7.
- At the end-of-treatment visit

14.5. QL assessment

In these patients, QL may be closely associated with the clinical efficacy of chemotherapy, functional status and psychological well-being (35). Key domains will be assessed by global linear analogue self-assessment (LASA) indicators: physical well-being defined as the primary QL endpoint (36), mood (37,38), coping effort (36,38) and overall treatment burden (39). Responses on these global indicators are expected to reflect the summation of the individual meaning and importance of various factors to each patient (40). These indicators are an alternative to a comprehensive standard assessment, as used for the comparison of paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer (41); such a comprehensive approach is better suited for less frequent assessments. In addition, specific LASA indicators based on the GLQ-8 (42) for appetite, tiredness, hair loss and feeling sick (nausea/vomiting) will be included with an adapted wording. Finally, sensory neuropathy will be assessed by the 4-item subscale of the FACT/GOG-Ntx (43). This subscale is an efficient alternative in measuring this toxicity in clinical trials (44,45). The QL indicators are comprised in a one-page questionnaire. Patients need only a few minutes to complete it. The LASA indicators range from 0 to 100. The FACT/GOG-Ntx subscale for sensory neuropathy range from 0 to 16. For all QL measures higher scores reflect a better condition (e.g., better physical well-being).

14.6. Statistical considerations

The QL portion of this trial is designed to assess patient-reported well-being, symptoms and side-effects over time for patients treated with three different schedules of nab-Paclitaxel as first-line therapy in metastatic breast cancer. The primary QL endpoint is physical well-being. We hypothesize that QL changes over time. We will examine this

hypothesis using a repeated measures model, controlling for stratification factors. Treatment will be included as a within-subject covariate with the identical values corresponding to the assessments of the first 3 induction cycles and the actual treatment assignment corresponding to the rest of the assessments. A covariate indicating different starting dose in induction (150 mg/m^2 vs 125 mg/m^2) will also be included. All patients with at least one QL assessment will be included into the analysis. This model will describe the effects of the randomized maintenance treatments on QL over the whole observation period. The impact of patients' age will be explored.

We suspect that the change in physical well-being from baseline to 6 months (24 weeks) after start of treatment differs between treatment arms. We consider statistical power based on the Wilcoxon rank sum test for comparing this change between treatment arms. Table 14 displays the effect sizes and powers for each pairwise treatment comparison, assuming a 25% or 40% missing rate across the treatment arms (i.e., 75% or 60% of patients having baseline and 24 week assessments) and a two-sided alpha-level of 0.05. Effect size is defined as the difference between two treatments arms of the change in physical well-being from baseline to 24 weeks divided by the common standard deviation of the two treatment arms. For example, assuming a 40% missing rate, a sample size of 86 (52 per arm) will achieve 80% statistical power to detect an effect size of 0. 57 between two arms using a two-sided 0.05 level Wilcoxon rank sum test. These power calculations do not adjust for multiple comparisons.

Table 14 – Effect Sizes by Statistical Power

N_1	N_2	Missing rate	80% Power	85% Power	90% Power
86	86	25%	.51	.55	.59
86	86	40%	.57	.61	.66

We hypothesize that QL differs from baseline to 6 months (24 weeks) after start of treatment in patients with CR/PR as compared to patients who have had SD for at least 6 months (or non-CR/non-PD in the case of non-measurable disease). We will test this hypothesis for the endpoints, physical well-being, mood and coping effort, using the Wilcoxon rank sum test. In addition, the change in physical well-being from baseline to 6 months after start of treatment will also be summarized for each treatment arm by different starting dose in induction (150 mg/m^2 and 125 mg/m^2) separately.

The association between the QL baseline scores and treatment feasibility (completing treatment according to the protocol for at least 24 weeks) will be examined by comparing QL baseline scores between feasibility groups using the Wilcoxon rank sum test for each treatment arm separately. This will also be done for each arm separately by different starting dose in induction (150 mg/m^2 and 125 mg/m^2).

Missing assessments may be due to stopping treatment, not completing the QL assessments, and other reasons. The reasons missing will be collected and reported.

14.7. Timing requirements

All QL questionnaires are to be completed during the patients' visits in the clinic. The schedule of QL assessment time points must be followed as closely as possible. Timing effects have an impact on patients' self-estimation of QL (46). It is important that the QL

questionnaire is completed before any diagnostic procedures or communication of diagnostic information to the patient (exception: baseline assessment) and before any administration of treatment. If, for administrative reasons, the form has not been presented to the patient, it may be filled in at home and mailed.

14.8. Data collection and local data management

For the first assessment, the QL questionnaire must be explained to the patient, with particular emphasis on making sure the patient understands both the LASA and the categorical response format. All questions must be answered. The completed questionnaire is to be checked while the patient is still present. If necessary, the patient should be asked to fill in missing answers. If the patient does not complete a scheduled QL assessment, an empty QL questionnaire should be faxed with the patient ID number and initials, the date the questionnaire was meant to be filled in, and the reason for not completing the questionnaire.

Questions regarding QL assessment may be addressed to the IBCSG QL Office (see contact person and address on front page).

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

The Investigator will ensure that this study 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 study 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. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

15.1. 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 ERB/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.

15.2. 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.

15.3. Protection of human subjects

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 subjects 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 15.4. Additional institution-specific sections should be added to Appendix I as described in Section 15.4.

The medical record must be available for review by the IBCSG audit team and regulatory authorities as described in Section 16.4.

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

15.4. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “IBCSG Patient Information 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. The patient should be told that material from her tumor will be stored and potentially used for additional studies not described in this protocol.

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. If the patient is legally incompetent (i.e., a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the Investigator agrees to conduct the trial in accordance with Good Clinical Practice 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 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.

15.5. Premature withdrawal

15.5.1. Withdrawal from trial treatment

Patients have the right to refuse further trial treatment at any time during the trial. Patients may also be withdrawn at any time from trial treatment 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 will be transferred to the follow-up phase. For the patient's safety, a last examination (end-of-treatment visit) should be performed and documented in the corresponding iDataFax forms.

15.5.2. 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 timepoint of withdrawal will continue to be evaluated in the trial. The Investigator should ask the patient for her consent to continue to collect information on her disease and survival status.

It should be documented in both the medical records and in the eCRF (Form 42-COC) whether it is acceptable for the patient to be contacted for survival status updates despite her withdrawal of study consent.

16. Governance and Administrative Considerations

16.1. 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 Group/Center should report all alleged claims immediately to the IBCSG.

The IBCSG insurance does NOT cover patients from the United States of America or from Canada.

16.2. Steering Committee

A Steering Committee will be constituted for this trial. The primary responsibilities of the Steering Committee are twofold. First, the Steering Committee 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. Second, the Steering Committee is responsible for translation of recommendations of the IBCSG Data and Safety Monitoring Committee into decisions. Membership will include IBCSG officials, study chair and co-chairs, trial statisticians, representatives from some participating Centers and Groups, and representatives from Celgene.

General partition of responsibilities:

The Steering Committee has the authority to make and implement any final decisions, such as substudies of the trial or amendments to the trial protocol, and may recommend the termination/early termination of the trial.

The IBCSG Executive Committee is responsible for the implementation of all final decisions taken by the Steering Committee.

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

16.3. Premature discontinuation of the trial

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

16.4. Quality assurance and monitoring

The IBCSG conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial IBCSG Data Manager reviews each CRF as it is received. In addition, the IBCSG Medical Reviewer reviews each case at specific timepoints. The IBCSG conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from IBCSG, Celgene Quality Assurance Group 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 study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits 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, nab-Paclitaxel administration, patient compliance with the regimens, drug accountability, concomitant therapy use and quality of data.

16.5. Data protection

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

Only the patient ID will be used to identify the patient on the CRF. 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, hospital number and the 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.

16.6. 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, drug inventory and destruction logs, 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.

Longer retention may be required for participating Centers according to national regulations.

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.

16.7. Confidentiality

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

17. References

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18. List of abbreviations

ADL	Activities of daily living
ATC	Anatomical therapeutic chemical
AE	Adverse event
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
NCI CTCAE	National Cancer Institute common toxicity criteria for adverse events
DCR	Disease control rate
DMC	Data Management Center (IBCSG)
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen receptor
FFPE	Formalin fixed paraffin embedded
FSTRF	Frontier Science and Technology Research Foundation
GCP	Good clinical practice
GI	Gastro-intestinal
H&E	Hematoxylin and eosin
HER2	Human epidermal growth factor 2
HR	Hazard ratio
IATA	International Air Transport Association
IBCSG	International Breast Cancer Study Group
IC	Informed consent
ICH	International conference on harmonization
iDF	iDataFax
LASA	Linear analog self-assessment
NYHA	New York Heart Association
OS	Overall survival
PFS	Progression-free survival
PgR	Progesterone receptor
PD	progressive disease
PR	Partial response
QC	Quality control
QL	Quality of life
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SD	Stable disease
SPARC	Secreted protein, acidic, cysteine-rich (osteonectin)
SPC	Summary of product characteristics
TL	Target lesions
ULN	Upper limit of normal
UN	Unknown
USP	United States pharmacopeial convention