International Breast Cancer Study Group Statistical Center

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

NCT01746225

Version	Author	Date	Status
1	Zhuoxin Sun	01/03/2016	Final

1 INTRODUCTION

1.1 BACKGROUND

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. 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/m2 every 3 weeks) achieved significantly higher response rates and longer PFS compared with standard 3-weekly paclitaxel. More recently, a randomized study in first-line metastatic breast cancer demonstrated superior efficacy and safety of nab-Paclitaxel 150 mg/m2 on a weekly schedule, compared with docetaxel 100 mg/m2 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/m2 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.

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 Each of three arms will be compared to a historical reference of seven-month median PFS based on the most recent trial with docetaxel as control arm to determine whether any of the three arms are worthy of further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/m2 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.

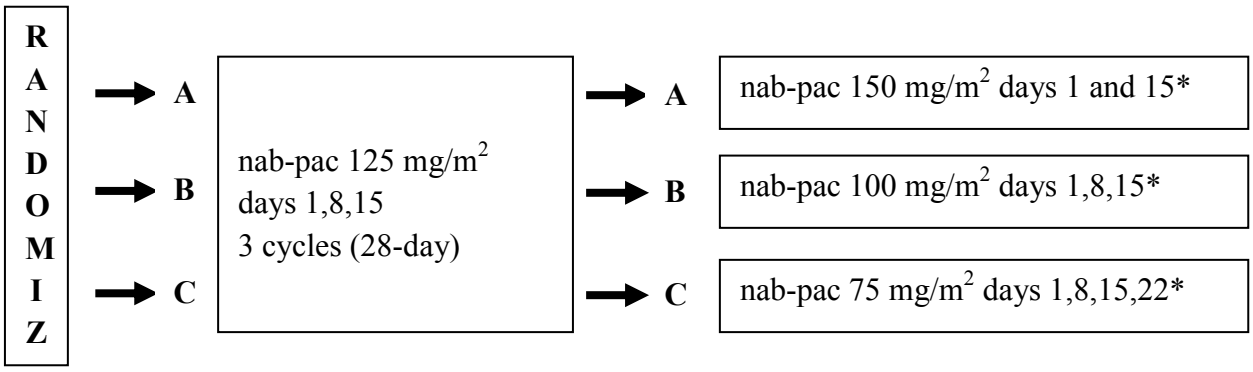
1.2 TRIAL DESIGN

SNAP (IBCSG 42-12/BIG 2-12) OVERVIEW

Title:	**SNAP:** A randomized phase II study evaluating three different schedules of nab-paclitaxel as first-line chemotherapy in metastatic breast cancer
Patient Population:	Patients with histologically or cytologically confirmed HER-2 negative metastatic (stage IV) breast cancer who have not received chemotherapy for

	metastatic breast cancer
Entry:	Patients must be randomized before receiving any chemotherapy for metastatic breast cancer. 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.
Activation Date:	31 October 2012 (first patient entered 16 April 2013)
Target Accrual:	258 patients
Closure Date:	7 August 2015 (Last patient entered 7 August 2015)
Final Accrual:	258 patients

Trial Schema:



*Continue treatment until progressive disease (PD) or unacceptable toxicity. Tumor evaluations are required every 3 months.

Randomization is 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.

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, assumed as median of 7 months. A total of 258 patients will be stratified and randomized in a 1:1:1 allocation, which will result in approximately 86 patients in each arm.

1.3 STATISTICAL DESIGN AND SAMPLE SIZE

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).

1.4 TRIAL CONDUCT

1.4.1 Protocol Versions/Amendments

Amendment 1: In the original design of this phase II trial, the induction phase planned three cycles of nab-Paclitaxel 150 mg/m^2 days 1, 8, 15 every 28 days. Following the first safety review of 48 treated patients, it was decided to modify the dose in the induction phase to 125 mg/m². The change was included in Amendment 1 (dated 11 August 2014) and this amendment was activated on 5 September 2014. A letter, dated 30 June 2014, was distributed to investigators alerting them to the planned amendment and indicated that the reduction to 125 mg/m2 as initial dose should be implemented IMMEDIATELY; for ongoing patients who were still at the 150 mg/m2 dose in the induction phase, the decision to decrease the next dose to 125 mg/m2 or continue with the 150 mg/m2 dose was left to investigator discretion.

Amendment 2: Based on recommendations from the October 2014 DSMC meeting, IBCSG has decided to increase the total sample size from 240 to 258. The statistical considerations (power calculations) in the protocol have been adapted accordingly. The original statistical design required 76 patients per arm in order to have, within a reasonable follow-up time, the 63 progression-free survival (PFS) events per arm needed to provide the planned power. The sample size considerations additionally assumed 5% “drop-out” (i.e., patients who will not ever contribute PFS events) so that accrual of 80 patients per arm (240 total) was planned. Thus, 12 total drop-outs were anticipated. As of 19 November, 2014, 9 such “drop-outs” had been documented. Considering the first 87 patients enrolled prior to April 2014 who have longer follow-up, the drop-out rate was 9.2% (8 of 87 patients). Thus as longer follow-up accumulates, the rate of “drop-out” is anticipated to rise to as much as 12%. To obtain the originally planned power, the accrual per arm will therefore be increased to 86 patients (76/0.88 = 86.4). The follow-up time is increased to 16-18 months after enrollment of the last patient, the total duration of the trial remains at 4 years. Those changes were included in Amendment 2 (dated 6 January 2015) and this amendment was activated on 23 January 2015.

2 EFFICACY ANALYSIS PLANS

2.1 OBJECTIVES

2.1.1 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.

2.1.2 Secondary objectives

- Tolerability
- Feasibility
- Disease response according to RECIST criteria, 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.

2.2 ANALYSIS POPULATIONS

Randomized population: All patients randomized to SNAP.
Treated population: All patients receiving at least one dose of trial treatment.

2.3 ENDPOINT DEFINITIONS

2.3.1 Primary Endpoint

Progression-free survival (PFS) is defined as time from randomization until objective disease progression according to RECIST 1.1 criteria or death, whichever occurs first. For patients without progression, follow-up will be censored at the date of 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.

For patients with documented disease progression:

- The PFS event date is the date progression was first documented by radiological assessment(s);
    - in case of a suspected new lesion that is documented at next TEV, then PFS date is that of first detection of new lesion;
    - in case of an equivocal finding that is unequivocal progression at next TEV, then PFS date is that of the first equivocal finding;

- in case the multiple assessments for the sum of target lesion measurements are done on different dates, then PFS event date is the date of the last assessment of target lesions that shows the predefined increase in sum of target lesions.

For patients without documented disease progression at time of trial treatment discontinuation, follow-up on the same schedule (every 12 weeks +/- 2 weeks) will continue until documented progression or the time of trial analysis. For patients without documented disease progression and are still alive when the trial analysis is conducted (i.e., data cutoff), PFS will be censored at the date of last adequate disease assessment.

For patients died, if death occurs within a short period of time following the date of disease assessment (12 weeks, corresponding to the interval of tumor re-evaluation), then the death will be counted as a PFS event, using date of death as the PFS event date; otherwise PFS will be censored at date of last adequate disease assessment.

If non-protocol therapy (systemic, radiation or surgical anti-tumor therapy that affects the tumor evaluation using RECIST criteria) is initiated, patients will be followed for documented progression.

Patients with new (non-breast) cancer malignancy must continue to be followed for progression of the original breast cancer.

If a patient withdraws consent or is lost to follow-up prior to documented disease progression, then PFS is censored at the date of last adequate disease assessment (NOT date WC nor date last contact when LFU).

If the only adequate disease assessment is the baseline assessment, then PFS is censored on day 1 (except in the situation of death that occurs within first 12 weeks, which is considered an event).

The investigator-provided documentation of progression, deaths, adequacy of disease assessments, and use of non-protocol therapy prior to documented progression, are being reviewed by the DMC and Medical Affairs; both are blinded to treatment assignment during the review. The data source of PFS events/censoring will therefore be the Internal Response CRF (53-IR).

Sensitivity Analysis of PFS will be discussed in Section 2.5.3.3.

2.3.2 Secondary Endpoints

- Tolerability: adverse events according to CTCAE version 4.

Each AE recorded over time will first be summarized as the maximum grade of the AE during the relevant time period, without regard to relation to trial treatment; patients' maximum grade of any AE over time will also be summarized.

Maximum grade consolidates the reports of a given type of AE for a patient over time by taking the maximum across time; grade 0 indicates no report of the given type of AE.

Patients' maximum AE grade consolidates the reports of all AE types for a patient over time; grade 0 indicates no AEs have been reported for the patient.

- Feasibility: Feasibility is defined as whether or not the patient completes 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) for a duration of ≥24 weeks, or better (i.e., partial or complete response) according to RECIST criteria

Best overall response: best response recorded from the start of treatment across all time points until end of study treatment. 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.

Duration of response: 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.

- Overall survival: time from randomization until death from any cause, or will be censored at date last known alive.
- QL endpoints

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

- Prognostic marker endpoints

The expression of SPARC and caveolin

2.4 FOLLOW-UP

The follow-up will be ceased when the number of PFS events in each arm reaches 63 (as detailed in Section 1.3), which was expected, as described in the protocol, approximately when the last randomized patient has at least 16-18 months follow-up from randomization. The final analysis will be performed at that time. Based on data as of December 31, 2015, the targeted number of events could be reached around the second quarter of 2016, earlier than expected.

Patients should be followed through the end of the trial 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. After progression patients will be followed for survival status only.

2.5 ANALYSIS COMPONENTS

2.5.1 Enrollment, Eligibility, Follow-up Compliance

2.5.1.1 Enrollment

Tables:

Dates first and last patients randomized

Number of centers randomizing patients, total and by cooperative group/country

Number of patients randomized in each participating centers by cooperative group/country, over time (by year)

Number of patients randomized in each cooperative group/country, overall and according to stratification factors

Distribution of stratification factors, overall and according to treatment assignment

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

Figure: Number of patients accrued by month

2.5.1.2 Eligibility

Tables:

Number of eligible patients and reasons ineligible, by treatment arms

2.5.1.3 Follow-up

The median follow-up on patients treated and still alive. Numbers of patient withdraw consent/lost to follow-up (with progression information vs. without progression information)

A CONSORT diagram will be given: For each treatment arm, number of patients randomized, number of patients eligible, number of patients started induction treatment, number of patients completed induction treatment, number of patients stopped during/after induction treatment, number of patients started maintenance treatment, number of patients still on maintenance treatment; number of patients completed maintenance treatment, number of patients WC/LFU.

2.5.2 Patient, Disease and Prior Treatment Characteristics

The treated patients population will be included in the analysis.

Table: Tabulate the following variables overall and by treatment arm. Continuous variables will be summarized as mean, SD, minimum, maximum. Categorical variables will be summarized as frequencies and percentages.

1. Patient and disease characteristics

Race
Age at randomization (>=70 vs <70)
BMI
Performance status
ER status (ER-negative or ER-positive) based on metastatic biopsy if available or otherwise the primary tumor
Measurable or non-measurable disease according to RECIST
Primary breast cancer
ER status
PgR status
HER2 status
Metastatic breast cancer
Number pts having mx disease biopsied
ER status
PgR status
HER2 status
Presence of visceral metastasis (liver and/or lung)
Number of metastatic sites

2. Prior Treatment

Patients had primary breast cancer diagnosed and treated prior to metastatic breast cancer
Duration (years) from diagnosis of primary breast cancer to metastasis breast cancer
Primary Tumor: prior endocrine therapy
SERM
Aromatase Inhibitor
GnRH or LHRH agonist
Other endocrine therapy for Primary
Primary Tumor: prior chemotherapy
Anthracycline
Taxane
Other chemotherapy
Metastatic Tumor: Prior Endocrine Therapy
SERM
Aromatase inhibitor
GnRH or LHRH agonist
Fulvestrant
Other endocrine therapy for metastatic breast cancer
Duration (years) of endocrine therapy for metastatic disease
ER- patients
prior chemotherapy (yes vs. no)

ER+ patients
Prior chemotherapy (yes vs. no)
Endocrine Therapy in adjuvant setting,
Endocrine Therapy in adjuvant and metastatic setting
Endocrine Therapy in metastatic setting only

3. Baseline AEs

2.5.3 Primary Efficacy Analysis

2.5.3.1 Tests and Estimates

The treated patients population will be included in the analysis.
For each arm separately, PFS will be compared to the historic PFS of first-line docetaxel using a one-sample two-sided log-rank test, of the null hypothesis, H0: median PFS≤7 months vs H_1: median PFS>7 months. . PFS distribution 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/m2 and 125 mg/m2).

2.5.3.2 Tables and Figures

Tables:

For each treatment arm: the numbers of patients and PFS events, Median PFS and two-sided 90% CI and the one-sample log-rank test statistic and p-value comparing to the historical PFS.

The numbers of patients and PFS events, Median PFS and two-sided 90% CI by treatment arms, for each starting dose level separately.

Figures:

K-M figures of PFS will be given by treatment arms for all patients, and also by different starting dose level. Y-axis is percent of patient alive and free from progression (range 0-100); x-axis is months since randomization; numbers of patients at risk will be provided.

2.5.3.3 Sensitivity Analyses

2.5.3.3.1 A sensitivity analysis of PFS will be conducted where patients receiving non-protocol, anti-tumor treatment prior to progression will be censored at the time of non-protocol treatment starts.

2.5.3.3.2 For those who entered maintenance phase, PFS will be also calculated from the start of the maintenance treatment. Numbers of patients and PFS events, Median, two-sided 90% CI and K-M plots will be given by treatment arm.

2.5.3.4 Subgroup Analysis

Numbers of patients and PFS events, Median PFS and two-sided 90% CI, K-M figures will be given for each treatment arms by ER status (ER-negative vs ER-positive), prior adjuvant taxanes in the neoadjuvant or adjuvant setting (yes vs no), and measurable or non-measurable only disease, age (>=70 vs <70), presence of visceral metastasis (yes vs. no), number of metastatic sites (1-3 vs. >3) separately.

2.5.4 Secondary Efficacy Endpoints

2.5.4.1 Tolerability

Please see Section 2.5.5.

2.5.4.2 Feasibility

The treated patients population will be included in the analysis.

Feasibility is summarized by the percentage of patients who complete treatment according to the protocol (including treatment reduction/delay) for at least 24 weeks. The percentages will be summarized by treatment arm with two-sided 90% CI. The percentages of the feasibility will also be summarized for each arm separately by different starting dose in induction (150 mg/m2 and 125 mg/m2).

Table:

N, percentage by treatment arms, and by different starting dose in induction separately.

2.5.4.3 Disease Response

2.5.4.3.1 Tests and Estimates

Treated patients population will be included in the analysis.

Best overall response (CR, PR, SD, PD, NE), DCR, and the overall response after the 3 cycles of induction therapy will be summarized for each arm, and also separately by different starting dose in induction (150 mg/m2 and 125 mg/m2). Among the patients who experience a CR or PR, the distribution of duration of response will be summarized using the method of Kaplan-Meier for each arm separately; the timing at which response is achieved (i.e., the start of the duration of response interval) will be summarized descriptively.

Tables: N, percentage, two-sided 90% CI will be given by each treatment arm, and also separately by different starting dose in induction.

Figures: K-M plots of duration of response will be given by each treatment arm, and also separately by different starting dose in induction. Y-axis is percent of patients free from progression (range 0-100); X-axis is months since response; numbers of patients at risk will be provided.

For patients with measureable disease, a waterfall plot of maximum tumor shrinkage (changes in tumor size from baseline to minimum tumor sum) will be given, color coded according to best overall responses status and treatment arms. This will also be done

separately by different starting dose in induction. Y-axis is maximum % change of target lesions; x-axis denotes each patient.

2.5.4.4 Overall Survival

2.5.4.4.1 Tests and Estimates

Treated patients population 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/m2 and 125 mg/m2).

Tables:

Numbers of patients and deaths, Median OS and two-sided 90% CI by treatment arms,

Numbers of patients and deaths, Median OS and two-sided 90% CI by treatment arms, for each starting dose level separately.

Figures: K-M figures of OS will be given by treatment arms for all patients, and also by different starting dose level. Y-axis is percent of patient alive (range 0-100); x-axis is months since randomization; numbers of patients at risk will be provided.

2.5.4.4.2 Sensitivity Analyses

For those who entered maintenance phase, OS will be also calculated from the start of the maintenance treatment. Numbers of patients and deaths, Median, two-sided 90% CI and K-M plots will be given by treatment arm.

2.5.4.4.3 Subgroup Analysis

Numbers of patients and deaths, Median OS and two-sided 90% CI, K-M figures will be given for each treatment arms by ER status (ER-negative vs ER-positive), prior adjuvant taxanes in the neoadjuvant or adjuvant setting (yes vs no), measurable or non-measurable only disease, age (>=70 vs <70), presence of visceral metastasis (yes vs. no), number of metastatic sites (1-3 vs. >3) separately.

2.5.5 Adverse Events / Safety

2.5.5.1 Population

All treated patients will be included.

2.5.5.2 Analysis

Tables:

The frequencies (Ns and %s) of adverse events (AE) (targeted and other AEs, without regard to relation to trial treatment) while on treatment will be summarized and tabulated by grade. For targeted AEs, the maximum grade will be summarized by AE type. The AEs will be also summarized on a per-patient basis, including patients' maximum grade of all AE types.

Separate tabulations will include the AEs reported during the induction phase (combing three arms), the events reported during the maintenance phase (by treatment arms). These tabulations will also be done separately by different starting dose in induction (150 mg/m2 and 125 mg/m2).

For neutropenia and sensory neuropathy, the two frequently-observed AEs in patients receiving nab-Paclitaxel, the two-sided 90% CIs of grade 3-4 neutropenia rate and grade ≥ 2 sensory neuropathy rate will be provided by treatment arm, and also separately by different starting dose in induction.

2.5.6 Treatment

2.5.6.1 Protocol-assigned treatment

All treated patients will be included.

Tables:

Treatment information for the induction phase of the trial (combing three arms, but separately by different starting dose levels in induction): N of patients discontinued, N of patients had dose reduction/omission; the reasons; the cycle that the first dose reduction/delay/omission/discontinuation due to toxicity was occurred.

The dose intensity within 4 weeks and dose intensity within 12 weeks during the induction phase (by different starting dose levels in induction). Dose intensity within 4 weeks is the average amount of drug delivered per week over the first 4 weeks after induction treatment started. Dose intensity within 12 weeks is the average amount of drug delivered per week over the first 12 weeks after induction treatment starts. The protocol-scheduled dose intensity should be 112.5 mg/m2 (if 150 mg/m² as the starting dose) and 93.8 mg/m2 (if 125 mg/m² as the starting dose).

Treatment information for the maintenance phase of the trial (by treatment arms): N patients initiating maintenance; N of patients discontinued, N of patients had dose reduction/omission; the reasons.

Duration of treatment will be defined as the time from the induction treatment until the study treatment discontinuation. For those still on treatment, they will be censored at the last known treatment date.

Duration of maintenance treatment will be defined as the time from the maintenance treatment until the study treatment discontinuation. For those still on treatment, they will be censored at the last known treatment date.

Figures: K-M plots of duration of treatment (and duration of maintenance treatment) will be given by each treatment arm, and also separately by different starting dose in induction. Y-axis is percent of patient receiving treatment (range 0-100); X-axis is months since start of treatment.

Cumulative incidences of treatment discontinuation (maintenance treatment discontinuation) will also be calculated with PFS as competing events. Cumulative incidence plots will be provided.

2.5.6.2 Non-protocol treatment

The numbers of patients receiving non-protocol anti-tumor treatment will be summarized by treatment arm.

Table: N, % (the total number of patients in each arm as denominator) will be given by treatment arms.

3 QUALITY-OF-LIFE / CORRELATIVE / TRANSLATIONAL

More details will come later for this section. Below are the sections from the protocol.

3.1. QUALITY-OF-LIFE

3.1.1 Overview

The objectives are 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 used at randomization. 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/m2 vs 125 mg/m2) 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 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/m2 and 125 mg/m2) 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/m2 and 125 mg/m2).

Reasons of missing assessments will be summarized.

3.2 Correlative / Translational

3.1.1 Overview

The expression of SPARC and caveolin will be compared between the primary and metastatic sites using Wilcoxon signed rank test.

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). We will compare PFS between the high-SPARC patients and low-SPARC patients.

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.

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.

4 VARIABLES

Variable	CRF	Field	Formulas for derived variables
Patid			
Treatment arm	A		A, B, C
Date of randomization	A		
ER status at randomization	A	A6	
Prior taxanes	A	A7	
Measurable disease	A	A8	
Age at randomization	A	A9	
race	H	H1	
BMI	H	H2 H3	derived
ECOG PS	CT	CT3	
eligibility	ER		derived
treated	IR	IR1	
Dose_level	CT	CT9 (ids1/ads1)	Starting dose level
WC status	Master		
Survival status, date	Master		
Baseline targeted AEs	BS	BS1-16	
Baseline other Aes	BS	BS17	
PFS	IR	IR3, 5	Combine progression and death info
PFS indicator	IR	IR1	
PFS2	IR	IR3-5	Combine progression, non-protocol treatment and death info

Variable	CRF	Field	Formulas for derived variables
PFS2 indicator	IR	IR1	Combine progression, non-protocol treatment and death info
Maintenance start, date	CT	CT10	Derived For cycle 4, t1ads/ t1ids>0, t1atdc
Treatment duration	CT and TC	CT9 TC2	Derived TC2 date –CT9 date
Best response	IR	IR2	
Disease control	IR	IR2 IR3	Derived
Duration of response	IR	IR2, IR3	derived
Targeted AEs	AE	AE1-16	
Other AEs	AE	AE17	
Non-prot treatment Received	IR	IR4	Yes vs. no
Off treatment reason	TC	TC3	
Treatment reduction/omission	TC	TC9	Derived, combine reduction/omission
Treatment discontinuation during induction	CT	CT8	
Treatment reduction/omission reason	CT	CT8	
Total cycle received	CT	Last CT form	derived
Dose level	CT	CT8	
Dose intensity within 4 weeks	CT	CT8	derived
Dose intensity within 12 weeks	CT	CT8	derived
QL baseline	QLC		
QL during treatment	QLC		
QL missing reason	QLC	irnc	