Final Statistical Analysis Plan for BL12

A MULTICENTRE RANDOMIZED PHASE II TRIAL COMPARING NAB-PACLITAXEL TO PACLITAXEL IN PATIENTS WITH ADVANCED UROTHELIAL CANCER PROGRESSING ON OR AFTER A PLATINUM CONTAINING REGIMEN CCTG TRIAL BL12

SUPPORTED BY: Celgene

Prepared by:

Trial Statistician: Keyue Ding, Ph. D

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1. Introduction and background

BL12 is a randomized, open-labelled, multicentre trial for patients with advanced urothelial cancer failing one line of platinum based therapy were randomized to either nab-paclitaxel or paclitaxel with a 1:1 ratio. The primary objective is to compare progression free survival (PFS) between treatment arms among all randomized patients. Patients were randomized stratified by study center, performance status (0,1 vs. 2), liver metastases (yes vs. no), lymph node metastases only (yes vs. no), hemoglobin (< 100 g/L vs. ≥ 100 g/L) and interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months). Secondary objectives include comparing overall survival (OS), objective response rate (ORR), clinical benefit rate (ORR+SD ≥ 12 weeks), time to response and response duration, safety and tolerability, QoL outcomes, and an economic analysis. Exploratory objectives include correlative biology (biological specimens and questionnaire) studies.

1.1 Study plan and its amendment, and interim analyses during the Conduction

Assuming a median progression free survival of 4 months with paclitaxel, the study was designed to detect a one third reduction in the hazard of disease progression with nab-paclitaxel (PFS HR=0.67) which translates into a 50% median PFS improvement of 2 months (i.e. from 4 to 6 months). Using a 1- sided 5% significance test with 80% power, 155 events are required. This would be achieved with an accrual rate of 5.5 patients/ month for 36 months with a follow-up period of 4 months. The estimated sample size is approximately 199 patients which would allow for a 5% lost to follow-up or withdrawal of consent.

The trial was activated on Jan. 27 of 2014, and the patient's accrual is still ongoing with 174 already been accrued to trial by Nov. of 2016. There is no interim analysis for this trial. This document is to describe the statistical analysis plan for the final analysis of the study. The analysis will include the primary and secondary efficacy endpoints, safety and QoL analysis, while the economic analysis and correlative study will be analyzed separately.

2. Methods and Analyses

2.0 Dataset

Clinical data cutoff date for patients included in this analysis, and date of freezing dataset will be given.

2.1 Analyses populations

Analysis populations for this analysis will be included both the intention to treat (ITT) population (i.e. all as randomized patients) and as treated population with data included as specified by the data cutoff point for this analysis.

Analysis of pretreatment characteristics and all other efficacy analysis such as PFS, OS, ORR, and other efficacy outcomes will be based on ITT population. While for safety analyses, it will be based on patients who have received at least one dose of study medication, i.e., as treated population.

2.2 Conventions for Calculating Key Data

Baseline evaluations are those collected closest, but prior to or on the day of randomization.

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoints within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of July of the year will be used to replace the missing day.

2.3 Analysis Conventions

All comparisons between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. There are no formal adjustments will be made for the multiplicity of inferences for other multiple clinical endpoints. Thus, if the primary endpoint is not significant at the 5% 1-sided test, the rest of the analyses are purely exploratory in nature.

The following baseline factors that will be used to adjust the analyses where appropriate are listed as follows: ECOG performance status (0,1 vs. 2), liver metastases (yes vs. no), lymph node metastases only (yes vs. no), hemoglobin (< 100 g/L vs. ≥ 100 g/L) and interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months) (*Add missing/unknown category whenever appropriate).

2.4. Randomization and Pre-treatment Characteristics

2.4.1 Definitions and Variables

2.4.1.1 Accrual

X Number (%) of randomized patients per study center. (Table 1)

2.4.1.2 Randomization/Stratification

X ECOG performance status (0,1 vs. 2),
X liver metastases (yes vs. no),
X lymph node metastases only (yes vs. no),
X hemoglobin (< 100 g/L vs. ≥ 100 g/L) and
X interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months). (Table 2)
(Note: An unknown/missing category will be added to each factor whenever is necessary.)

X Treatment assigned at randomization will be compared with the actual treatment received during the first cycle to identify any discrepancies (Table 3)

X Baseline patient characteristics will be compared with the patient's corresponding stratification assignment to identify any discrepancies (Table 4)

2.4.1.3 Ineligibility and Significant Protocol Deviations (Table 5)

X Eligible patients: % yes, no

X Reasons for ineligibility: % for each reason and combination of reasons of ineligibility. The process for verifying eligibility criteria is detailed in the data management plan for this study. In the final report, a distinction between minor deviation and truly ineligible will be made. Only those categories with truly ineligible patients will be included in the table.

2.4.1.4 Summary of Follow-up

A table showing the median, min and max follow-up will be presented by treatment group and for all patients included in analysis. (table 6)

2.4.1.5 Patient Characteristics

X Race: % Caucasian, African American, Asian, Hispanic or Latino, others, unknown (or refusal)
X Age: < 40 vs 40 to <50 vs. 50 to < 60 vs 60 to < 70 vs. 70+.
< 65 vs. ≥ 65, median, min and max;
X Gender: # (%), Male vs. Female;
X Prior Immunotherapy (No vs. Yes) (Table 7).

*Add missing or unknown as a category where it is appropriate.

2.4.1.6 Baseline symptoms (Table 8)

The CTC version 4.0 will be used for the categorization of all baseline symptoms.

X Any event per patient: % yes, no
X Type of event by grade (1, 2, 3, 4, unknown)

2.4.1.8 Baseline Hematology/Biochemistry (Table 9)

CTC grades will be used to summarize the baseline hematology/biochemistry data.

% by CTC grades

X WBC
X Anemia
X platelets
X Neutrophils
X Serum creatinine
X bilirubin
X ALT (SGPT)

2.4.2 Analysis of pre-treatment characteristics

No formal statistical tests will be performed to assess homogeneity of baseline characteristics between the arms. Categorical variables will be tabulated by treatment arm and for all patients. Continuous variables (e.g., age) will be presented using summary statistics (n, median, min and max) or specified cutoff categories by treatment arm and for all patients. Analyses will be based on all randomized patients by arm based on the ITT population.

2.5 Efficacy

2.5.1 Definitions and Variables

2.5.1.1 Progression free survival

Progression free survival is defined as the time from randomization to the date of the first documented disease progression or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for UC, prior to documentation of disease progression or death, will be censored on the last date of assessment prior to receive alternative therapy when there was no documented disease progression. If a patient has not progressed, died, or received alternative therapy for UC, PFS will be censored on the date of the last disease assessment.

2.5.1.2 Overall survival

Overall survival is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive.

2.5.1.3 Clinical benefit response rate

The clinical benefit response rate will be calculated for all patients. It is defined as the ratio of the total number of patients who achieve a complete or partial response (patients with at least one measurable lesion at baseline) plus those patients who have stable disease for at least 12 weeks (all patients - with or without measurable disease at baseline**)** based on the Response Evaluation Criteria in Solid Tumours – RECIST criteria to all randomized patients by treatment arm.

2.5.1.4 Objective response rates (complete or partial response (ORR))

Objective response rates (complete or partial response (ORR)) will be calculated for all patients. It is defined as the ratio of total number of patients who achieve a complete or partial response (patients with at least one measurable lesion at baseline) based on the Response Evaluation Criteria in Solid Tumours – RECIST criteria to all randomized patients by treatment arm.

2.5.1.5 Time to response

Time to response is defined as the time from the date of the first dose of study drug until the first objective status assessment of CR/PR among those who achieved a CR or PR. For the rest of patients, it will be censored at last disease assessment date.

2.5.1.6 The duration of response

The duration of response is defined as the time from the date of the first documentation of CR or PR to the time disease progression or death is documented (whichever comes first). A patient who stops treatment with study drug and goes on to receive alternative therapy for UC, prior to documentation of disease progression or death, will be censored on the date alternative therapy began. If a patient has not progressed or died or received alternative therapy, the duration of response will be censored on the date of last known disease assessment.

2.5.2 Analysis of Key Parameters

The comparison between treatment arms will be carried out using a two-sided test at a 1-sided alpha level of 5% unless otherwise specified. All efficacy analyses will be presented by treatment arm.

2.5.2.1 Progression Free Survival

All randomized patients will also be included in the progression free survival (PFS) analysis. Kaplan-Meier curves for the distribution of PFS in each treatment arm will be displayed. The difference between survival distribution of the two treatment arms will be tested using the log-rank test stratified by: ECOG PS (0,1 vs. 2), liver metastases (yes vs. no), lymph node metastases only (yes vs. no), hemoglobin (< 100 vs. ≥ 100) and interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months). Estimate of hazard ratio (HR) and its 90% C.I. will be obtained from Cox regression stratified by the stratification factors except center. (Table 10).

Log-rank test will also be performed without adjusting those stratification factors.

In addition, the effect of study centre and other potential prognostic factors will be assessed using Cox regression analysis. The Schoenfeld [Schoenfeld 1982] residual plots will be used to check the proportional hazard assumption. The 95% confidence intervals for the median survival will be computed using the method of Brookmeyer and Crowley.

A table will be presented for the summary of types of progression by arm. For patients who did not progress, a table will be printed for the reasons for censoring, which includes receiving anti-cancer therapy for Urothelial carcinoma, prior to documentation of disease progression. (Table 11).

Subgroup Analysis: The analysis of PFS will be presented for each level of stratification factors, median PFS, and its 95% C.I., estimate of HR and its 95% C.I., p-value from the interaction test below. (Table 12)

Cox regression model with interaction terms included to test homogeneity of treatment effect across the level of stratification factors (Exclude those with missing).

Those factors are: ECOG PS (0,1 vs. 2), liver metastases (yes vs. no), lymph node metastases only (yes vs. no), hemoglobin (< 100 vs. ≥ 100) and interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months).

It should be pointed out that the main purpose for this section is to see if the treatment effects are homogeneous across the levels of each stratification factor. The sample size may not be large enough to detect a small or moderate difference in each subgroup.

The anti-cancer therapy received after the progression will also be tabulated (Table 13).

2.5.2.2 Overall survival

All analysis for PFS will be performed for OS. And a table summarizes the death causes by arm.
(Table 14-16).

2.5.2.3 Clinical benefit response rate

The Clinical benefit response rate for all evaluable patients will be calculated by treatment arm. Cochran-Mantel-Haenszel (CMH) test stratified for ECOG PS (0,1 vs. 2), liver metastases (yes vs. no), lymph node metastases only (yes vs. no), hemoglobin (< 100 vs. ≥ 100) and interval from last platinum based chemotherapy (≤ 6 months vs. > 6 months) will be used to test the difference between 2 treatment arms. (Table 17).

Multiple logistic regression was used to study the correlation between the response and the patients' baseline factors (table 18).

The Clinical benefit response rate by stratification factors are summarized in table 19.

2.5.2.4 Objective response rates

The same analysis for Clinical benefit response rate will be performed for ORR. (Table 20, 21).

2.5.2.5 Time to response

The median of time to response and its 95% C.I. will be presented, and the estimated HR and its 95% C.I. and p-value from log-rank test. (Table 21).

2.5.2.6 The duration of response

For the patients who had achieved CR/PR during the study, the median duration of response and its 95% C.I. will be presented by treatment. (Table 22).

2.6 Drug Exposure

2.6.1 Definitions and Variables

2.6.1.1 Duration of Study Therapy in months, cumulative dose

Duration of study therapy (weeks) is defined as the time from the first date the patients took Nab-Paclitaxel / Paclitaxel to the date of final dose given.

X Duration of study therapy (weeks) for all patients by treatment arms (Table 23): median, min and max; mean and STD.

2.6.1.2 Cumulative dose, dose intensity and relative dose intensity of Nab-Paclitaxel / Paclitaxel

The total of Nab-Paclitaxel / Paclitaxel doses taken by the patients is defined as the sum of Nab-Paclitaxel / Paclitaxel taken by patients during the duration of the study.

Dose intensity is defined as the cumulative dose received divided by the duration of the study therapy in cycles.

Relative dose intensity is defined as dose intensity divided by the dose prescribed for the duration of the study therapy (Nab-Paclitaxel 260mg/m^2, Paclitaxel 175mg/m^2 times the number of the cycles of the patient was on treatment).

- X Total of Nab-paclitaxel /paclitaxel doses (Table 23): median, min and max.
- X Dose intensity per patient during the study (Table 23).
- X Relative dose intensity per patient during the study (Table 23).

2.6.1.3 Dose reduction, interruption or discontinuation

Nab-Paclitaxel / Paclitaxel dose may be adjusted (reduced, interrupted or discontinued) because of toxicities or other reasons. The dose of a patient is considered to be reduced, interrupted or discontinued if there is a record in the reason for dose modification in Nab-Paclitaxel / Paclitaxel administration table in the treatment report form. Specifically, the dose of a patient is considered to be reduced if there is a record in the Dose (mg) column in the table which is less than planned dose but greater than 0 mg; the dose of a patient is considered to be interrupted if there is at least one record in the Dose (mg) column on the drug table which is equal to 0. The drug is considered permanently discontinued if there are reasons for Nab-Paclitaxel / Paclitaxel was permanently stopped in the end of treatment form. (Table 24)

- X Number of patients with at least one dose reduction, interruption during the study
- X Specify the primary reason for the dose reduction, interruption: % of patients with each reason (e.g., hematologic toxicity, administrative, etc.)
- X Number of patients whose dose was reduced at least once
- X Specify the primary reason for the dose reduction: % of patients with each reason (e.g., certain specific toxicity, administrative, etc.)
- X Specify secondary reason for dose reduction: % of patients with each reason (e.g., rash etc.)
- X Number of patients with at least one dose interruption
- X Specify reason for the dose interruption: % of patients with each reason (e.g., certain specific toxicity, administrative, etc.)
- X Specify secondary reason for dose interruption: % of patients with each reason (e.g., rash etc.)
- X Number of patients discontinued protocol treatment
- X Specify reasons for protocol treatment discontinuation: % of patients with each reason (e.g., progressive disease, intercurrent illness, etc.)

2.6.2 Analysis

All variables will be summarized for all treated patients by treatment received.

2.7 Safety

2.7.1 Definitions and variables

2.7.1.1 Laboratory tests

Analyses of laboratory data will include analyses of hematology and biochemistry tests. The hematology data include Anemia, WBC, platelets, neutrophils and the biochemistry data include ALT (SGPT), total bilirubin, serum creatinine (Tables 25-26). Laboratory results will be graded according to the CTC criteria version 4.0.

All laboratory data collected at any time during the study for these tests will be included in the analyses of worst value on study and those collected during a specific cycle for these tests will be included in the analyses of worst value during that cycle.

All tests specified above:

X CTC grade for worst value on-study (for hematology and biochemistry tests): %0, 1, 2, 3, 4

2.7.1.2 Toxicity/adverse event/intercurrent illness

The CTC version 4.0 will be used to summarize toxicities/adverse events/intercurrent illnesses. Events will be displayed by primary term. All toxicities/adverse events/intercurrent illnesses data collected during the trial will be included in the analyses of worst value on study, and data collected during a specific cycle will be included in the analyses of worst value during that cycle. All the analyses will be repeated to include only the toxicities/adverse events/intercurrent illnesses which are drug related (The relation to protocol therapy higher than or equal to 3).

- X Any event during the study (Table 27): % yes
- X Worst severity per patient per primary term on study (Table 27) (analysis per cycle will also be performed, table xx): % CTC grade 1, 2, 3, 4, unknown
- X Toxicity/adverse event/intercurrent illness which are serious (reasons for seriousness in the serious adverse event table for electronic SAEs and toxicity table higher than or equal to 1), fatal only; life threatening; leading to hospitalization; results in significant disability or incapacity; congenital anomaly; required intervention/important medical event, (Table 28).
- X Toxicity/adverse event/intercurrent illness that led to study drug discontinuation (Table 29)
- X Toxicity/adverse event/intercurrent illness that led to dose interruptions (Table 30)
- X Toxicity/adverse event/intercurrent illness that led to dose reduction (Table 31)

  Deaths within 30 days from last treatment administration (Table 32)

  Cause of death within 30 days from last treatment administration (Table 32).

2.7.2 Analysis

All patients who received at least one dose of study medication will be included in the safety analyses. Top 5 toxicities**,** and drug related grade 3 or higher will be compared using the Fisher's exact test for comparison of the toxicity rates between 2 treatment arms.

2.8 Concomitant medications, transfusion and hospitalization

2.8.1 Definition and Variables

Concomitant medications are all other medications (other than study drugs) taken at any time on-study. Hospitalizations are those which occur at any time on-study.

- X Any Antiemetics per patient (Table 33): % yes, no**.**
- X Any Growth Factors and Blood Products per patient (Table 33): % yes, no
- X Any Bisphosphonates and Bone Targeted Agents per patient (Table 33): % yes, no
- X Any hospitalization per patient (Table 33): % yes, no, Duration: Median and range.

2.8.2 Analysis

Supportive and concomitant medications and therapies will be displayed for all treated patients. The data will be presented as shown in the table samples in Table 33.

2.9 Off- protocol therapies

2.9.1 Definitions and Variables

- X Patients off- protocol therapies: Number and % of all randomized patients
- X Reason for going off- protocol therapies: Number and % of all randomized patients for each reason

2.9.2 Analysis

Tables will be presented by treatment arm and for all patients (table 34).

2.10 Quality of life

General QoL domains were assessed using the EORTC-C15-PAL questionnaire. This self-administered questionnaire is a shortened version of widely used EORTC-QLQ-C30. It consists of 15 items. Pain, physical function, emotional function, fatigue, global health status/quality of life, nausea/vomiting, appetite, dyspnoea, constipation, and sleep are retained. Four scales were shortened without reducing measurement precision. The validity and reliability of this questionnaire have each been established.

Since taxane-related peripheral neuropathy is an important symptom that adversely affects QoL in patients treated with either intervention, differences between arms in either the severity or duration of peripheral neuropathy would be important to detect. For this purpose, the FACT-Taxane questionnaire were added to the battery of Protocol Reported Outcomes (PROs). FACT-Taxane is a 16 item instrument that has been validated in patients with metastatic disease receiving taxane therapy, and has been shown to have excellent internal consistency, group validity, and responsiveness to change.

2.10.1 Definitions and Variables

2.10.1.1 EORTC QLQ- C15-PAL

EORTC QLQ-C15-PAL questionnaire is a short version of the QLQ-C30 for palliative care. The questionnaire includes four multi-item scales and six individual items. All items (except the global assessment, question no. 15) were scaled from 1 (not at all) to 4 (very much), in which a higher score indicates greater distress in symptom scales while a higher score in functional scale indicates greater functional ability. Each scale will be converted to a score ranging from 0 to 100.

If the number of unanswered questions in each domain is within a limit specified with the definition for each domain, the score is calculated as for function domains:
Score=100-(((Total score for the answered questions/(no. of questions answered))-1)*100/3)
And for symptom domains:
Score = (((Total score for the answered questions/(no. of questions answered))-1)*100/3)
Otherwise, the score will be recorded as “missing”. For each single item, the score will be recorded as “missing” if the answer to this item is missing.

Functional Domains/Symptoms items:

X Physical functioning: Questions: 1, 2, 3.
Score=missing if number of above questions not answered is greater than 1;
X Emotional functioning: Questions: 13, 14.
Score=missing if number of above questions not answered is greater than 0;
X Global: Question: 15
Score = ((Answred score for the questions-1)*100/6.

X Fatigue: Questions: 7, 11
Score=missing if number of above questions not answered is greater than 0;

X Nausea and vomiting: Questions:9
Score=missing if number of above questions not answered is greater than 0;

X Pain: Questions: 5, 12

Score=missing if number of above questions not answered is greater than 0.

X Dyspnea: Question 4;

Score=missing if the answer to the item is missing

X Insomnia: Question 6;

Score=missing if the answer to the item is missing

X Appetite loss: Question 8;

Score=missing if the answer to the item is missing

X Constipation: Question 10;

Score=missing if the answer to the item is missing.

2.10.1.2 The FACT-Taxane questionnaire

FACT-Taxane is a 16 item instrument that has been validated in patients with metastatic disease receiving taxane therapy, and has been shown to have excellent internal consistency, group validity, and responsiveness to change

Tax-subscale = ((The sum of 4 – item response score for all the answered items) / (no. of questions answered))*16 (Range 0 – 64).

Score=missing if more than 8 items are missing

2.10.2 Analysis

All analyses on quality of life scores will be exploratory and will include all randomized patients with at least 1 on study measurement besides the baseline evaluation.

2.10.2.1 Determination of Assessment Times

The following will be the scheme to determining the time frame of a QOL assessment:

1) Baseline: Baseline evaluation is the QOL questionnaire collected closest, but prior to, the first day of starting study treatment/randomization;
2) After completion of RT: If the QOL is assessed within 6 week of the date RT completion.
3) Every 6 months FU evaluation, Within 2 months of the scheduled time points.
4) At progression: If the QOL is assessed within 1 month when the progression is documented;

2.10.2.2 Calculation of Compliance Rates

Three methods will be used to calculate the compliance rates of QOL assessment. The first two are based on the number of forms received out of respectively all eligible patients enrolled into the study and all patients who had baseline QOL assessments. The last one is calculated as the number of forms received out of the number of forms expected at each assessment point defined based on the following principles:

1) At baseline: the number of forms expected is the total number of patients who are eligible for the study and required to fill out QOL questionnaires.
2) At days 5 -7 of cycle 1 and 2, day 1 of cycle 4 and then day 1 of every 4 cycles thereafter: the number expected is the total number of patients who are eligible, had baseline QoL data and completed the cycle of treatment;
3) At progression: the number expected is the total number of patients who are eligible, had baseline QoL data and has progressed;
4) At every 6 week visit FU period: the number expected at each assessment is the number of patients with baseline data minus the number of patients who have died or progressed during that and previous follow up period (Table 35).

2.10.2.3 Cross-sectional analysis

The mean and standard deviation of QOL scores at baseline (Table 36) and mean and standard deviation of QOL change scores from baseline (Table 37) at each assessment time will be calculated. Then Wilcoxon Rank-Sum test is used to compare two treatment arms in terms of change in QOL score at each assessment time from baseline (see Table 36).

2.10.2.4 QOL response analysis

QOL response is calculated as follows for a functional domain: A change score of 10 points from baseline was defined as clinically relevant. Patients were considered improved if reported a score 10-points or better than baseline at any time of QOL assessment. Conversely, patients were considered worsened if reported a score minus 10-points or worse than baseline at any time of QOL assessment without above specified 10-ponits improvement. Patients whose scores were between 10-point changes from baseline at every QOL assessment were considered as stable. In contrast to functional domains, for the determination of patient's QOL response, classification of patients into improved and worsened categories is revered for symptom domains and single items. Chi-square test is then performed to compare the distributions of these three categories between two arms and follow with a trend test to see if patients one study treatment arm had higher proportions with better QoL responses. **Note: For FACT-Taxane scale, we will use 6.5 instead of the 10 point in the response analysis.**

3. Tables

Table 1: Accrual by Center

Data set: All Randomized Patients			
	Number of patients (%)		
	Nab-Paclitaxel N = ***	paclitaxel N = ***	Total N = ***
Center #1	*** (**)	*** (**)	*** (**)
Center #2	*** (**)	*** (**)	*** (**)
Center #3	*** (**)	*** (**)	*** (**)
...	*** (**)	*** (**)	*** (**)

Table 2: Accrual by Stratification Factor at Randomization

Data set: All Randomized Patients

	Number of patients (%)		
	Nab- Paclitaxel N = ***	Paclitaxel N=***	Total N = ***
☐ ECOG PS			
0, 1	** (**)	** (**)	** (**)
2	** (**)	** (**)	** (**)
☐ liver metastases			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)
☐hemoglobin			
< 100	** (**)	** (**)	** (**)
≥100	** (**)	** (**)	** (**)
lymph node metastase only yes	** (**)	** (**)	** (**)
no	** (**)	** (**)	** (**)
Interval from last platinum based chemotherapy			
≤ 6 months	** (**)	** (**)	** (**)
> 6 months	** (**)	** (**)	** (**)

Source: Centralized Randomization File

Table 3: Treatment as Randomized Versus as Treated at Cycle 1

Data set: All Randomized Patients			
	Number of Patients (%) Randomized Arm		
	NAB-PACLITAX N=***	Paclitaxel N=***	Total N=***
Treatment Received			
NAB-PACLITAXEL	*** (**)	*** (**)	*** (**)
Paclitaxel	*** (**)	*** (**)	*** (**)
Not treated	*** (**)	*** (**)	*** (**)

Table 4: Discrepancies between Stratification Level as Randomized and at Baseline

Data set: All Randomized Patients						
	Number of patients (%)					
	NAB-PACLITAX N=***		Paclitaxel N=***		Total N=***	
Any difference	*** (**)		*** (**)		*** (**)	
At baseline	As Randomized		As Randomized		As Randomized	
☐ ECOG PS	0, 1	2	0, 1	2	0, 1	2
0, 1	**	**	**	**	**	**
2	**	**	**	**	**	**
hemoglobin	< 100	≥ 100	< 100	≥ 100	< 100	≥ 100
<100	**	**	**	**	**	**
≥100	**	**	**	**	**	**
liver metastases	Yes	No	Yes	No	Yes	No
Yes	**	**	**	**	**	**
No	**	**	**	**	**	**
lymph node meta only	Yes	No	Yes	No	Yes	No
Yes	**	**	**	**	**	**
No	**	**	**	**	**	**
interval from last platinu based chemotherapy	< 6M	≥ 6M	< 6M	≥6M	<6M	≥6M
≤ 6 Months	**	**	**	**	**	**
> 6 months	**	**	**	**	**	**

Table 5: Eligibility, Reasons for Ineligibility and Major Protocol Violations

Data set: All Randomized Patients			
	Number of Patients (%)		
	Nab- Paclitaxel N=***	Paclitaxel N=***	Total N=***
Eligible	*** (**)	*** (**)	*** (**)
Not Eligible	*** (**)	*** (**)	*** (**)
Reason for ineligibility			
<Reason 1>	**	**	**
<Reason 2>	**	**	**
...	**	**	**
Major protocol violation			
<violation 1>	**	**	**
<violation 2>	**	**	**
...	**	**	**

Table 6: Month of Last Follow-up for all Patients and min and max FU for alive patients

Data set: All Randomized Patients			
	Number of patients		
	NAB-PACLITAXEL	Paclitaxel	Total
Number of patients aliv	***	***	***
Follow Up time	Median, min, Max.	Median, min, Max.	Median, min, Max.

Table 7: Pretreatment Characteristics at Baseline

Data set: All Randomized Patients	Number of patients (%)		
	Nab- Paclitaxel N=***	Paclitaxel N=***	Total N=***
Gender			
Female	** (**)	** (**)	** (**)
Male	** (**)	** (**)	** (**)
Race			
White	** (**)	** (**)	** (**)
Black	** (**)	** (**)	** (**)
....	** (**)	** (**)	** (**)
Age (years)			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
≤ 65	** (**)	** (**)	** (**)
> 65	** (**)	** (**)	** (**)
Prior IO			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)

Table 8: Baseline Signs and Symptoms

Data set: All Randomized Patients (NAB-PACLITAXEL Arm)

	Number of patients (%) N=***					
	Worst grade					Any grad
	NR	1	2	3	4	
Patients with any sign/symptom at baseline	** (*	** (**	** (**	** (**	** (**	** (**)
Patients with particular sig symptom, within body system:						
Body System 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Body System 2[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a body system

NOTE: Same table to be made for Paclitaxel Arm

Table 8: Baseline Hematology/Biochemistry

Data set: All Randomized Patients			
	Number of Patients (%)		
	NAB-PACLITAX N = ***	Paclitaxel N = ***	Total N=***
WBC			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Anemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Neutrophils			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Platelet			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Serum creatinine			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)

bilirubin			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
ALT (SGPT)			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)

[1] Not done

Table 10: Log rank and Cox Regression Model for Progression Free Survival

Data set: All Randomized Patients

	Univariate Analysis[1]			Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors Baseline	Median Survival (Months	Hazard Ratio[4] (95% CI)	Log-rar p-vlau	Hazard Ratio[4] (95% C.I.	P-vlaue from Cox regression
Treatment arm			†0.***		0.***
NAB-PACLITAXEL	**.**	**.**		**.**	
Paclitaxel	**.**	(**.**,**.**		(**.**,**.*	
Prognostic factor 1			0.***		0.***
Level 1	**.**	NC [3]		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 2			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 3			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
…			0.***		0.***
...	**.**	NC		**.**	
...	**.**			(**.**,**.*	

(1) Stratified
(2) Stratified Cox regression with all factors included
(3) NC = not computed
(4) Hazard ratio of first category over second category

Figure 1: K-M curves of PFS by treatment arm

Table 11 Progression Summary

Data set: All Randomized Patients		
	Number of Patients (%)	
	NAB-PACLITAXE N=***	Paclitaxel N=***
Patients who progressed	*** (**)	*** (**)
Progression on study	**	**
Progression during follow-up	**	**
Death (without documented progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Received anti-cancer therapy before documented progression:		
Chemotherapy	**	**
Radiotherapy	**	**
Hormonal therapy	**	**
Immunotherarpy	**	**
....	**	**
Lost to follow-up	**	**
Not progressed	**	**

Table 12: Progression free Survival by Subsets

Data set: All Randomized Patients

Factors	Value	Nab- Paclitaxel N	Nab- Paclitaxel Median Survival 95% C.I.	Paclitaxel N	Paclitaxel Median Survival 95% C.I.	Hazard Ratio[(1)] 95% C.I.	Int-p-value
ECOG PS	0, 1	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.***
	2	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
liver metastases	Yes	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	No	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
hemoglobin	<100	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	≥100	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
lymph node metastases	Yes	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	No	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
lymph interval from last platinum based chemotherapy	≤ 6M	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	*0.***
	>6M	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	

(1) Nab- Paclitaxel over Paclitaxel hazard ratio (Unstratified)

Table 13: Anti-Cancer Therapy Received After Progression

Data set: All Randomized patients		
	Number of patients (%)	
	NAB-PACLITAX N=***	Paclitaxel N =***
Number of patients with any follow-up therapy	*** (**)	*** (**)
Chemotherapy (1)	*** (**)	*** (**)
EGFR inhabitor (1)	*** (**)	*** (**)
Radiotherapy (1)	*** (**)	*** (**)
Hormonal therapy (1)	*** (**)	*** (**)
Immunotherapy (1)	*** (**)	*** (**)
Other (1)	*** (**)	*** (**)

(1) Patients could have more than one type of therapy.

Figure 2: K-M curves of OS by treatment arm

Table 14: Log rank and Cox Regression Model for Overall Survival

Data set: All Randomized Patients

		Univariate Analysis[1]		Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors Baseline	Median Survival (Months	Hazard Ratio[4] (95% CI)	Log-rar p-vlau	Hazard Ratio[4] (95% C.I.	P-vlaue from Cox regression
Treatment arm			†0.***		0.***
NAB-PACLITAXEL	**.**	**.**		**.**	
Paclitaxel	**.**	(**.**,**.**		(**.**,**.*	
Prognostic factor 1			0.***		0.***
Level 1	**.**	NC [3]		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 2			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 3			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
…			0.***		0.***
…	**.**	NC		**.**	
…	**.**			(**.**,**.*	

(1) Stratified
(2) Stratified Cox regression with all factors included
(3) NC = not computed
(4) Hazard ratio of first category over second category

Table 15 Death Summary

Data set: All Randomized Patients		
	Number of Patients (%)	
	NAB-PACLITAXE N=***	Paclitaxel N=***
Patients who died	*** (**)	*** (**)
Death Causes		
Disease	**	**
Disease/treatment complication	**	**
Others	**	**

Table 16: Overall Survival by Subsets

Data set: All Randomized Patients							
		Nab- Paclitaxel		Paclitaxel			
Factors	Value	N	Median Survival 95% C.I.	N	Median Survival 95% C.I.	Hazard Ratio(1) 95% C.I.	Int-p-value
ECOG PS	0, 1	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.***
	2	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
liver metastases	Yes	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	No	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
hemoglobin	<100	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	≥100	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
lymph node metastases	Yes	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	No	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	
lymph interval from last platinum based chemotherapy	≤ 6M	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	0.**
	> 6M	**	*.** (*.**,*.**)	**	*.** (*.**,*.**)	*.** (*.**,*.**)	

(1) Nab- Paclitaxel over Paclitaxel hazard ratio (Unstratified)

Table 17: Clinical benefit response rate

Data set: All Randomized Patients

	Number of Patients (%)* N=***	
	NAB-PACLITAXE N=***	Paclitaxel N=***
Patients with at least one target lesion**	N=***	N=***
Complete response (CR)	** (**)	** (**)
Partial response (PR)	** (**)	** (**)
Stable disease (SD)	** (**)	** (**)
Progressive disease (PD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Patients with no target lesions***	N=***	N=***
Complete response (CR)	**	**
Stable Disease (SD)	**	**
Progressive disease (PD)	**	**
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....

* percentages are calculated out of the number of patients in each category

** only patients with at least one target lesion are evaluable as defined by RECIST

*** patients with non-measurable disease only were followed for complete response, and disease progression. Patients who were assessed but did not meet the definition of CR or PD were recorded as SD.

Table 18: Cochran Mantel Haenszel and Logistic Regression Model for Clinical benefit response rate

Data set: All Randomized Patients

	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factc	Odds Ratio (95%CI)	CMH p-vlaue	Odds Ratio (95% C.I.	p-value from logisti regression
Treatment arm		0.***		0.***
NAB-PACLITAXEL : *Paclitaxel*	**.** (**.**,**.*		**.** (**.**,**.*	
Prognostic factor 1		0.***		0.***
Level 1: level 2	NC [3]		**.** (**.**,**.*	
Prognostic factor 2		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
Prognostic factor 3		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
…		0.***		0.***
...	NC		**.** (**.**,**.*	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 19: Clinical benefit response rate According to Baseline Stratification Factors

	Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)		
	Nab-Paclitaxel N=***	*Paclitaxel* N=***	*Int-P-value*
ECOG performance status			0.**
0+1	**/** (**)	**/** (**)	
2+	**/** (**)	**/** (**)	
liver metastases			
Yes	**/** (**)	**/** (**)	0.**
No	**/** (**)	**/** (**)	
lymph node metastases only			
Yes	**/** (**)	**/** (**)	0.**
No	**/** (**)	**/** (**)	
hemoglobin			
< 100	**/** (**)	**/** (**)	0.**
≥ 100	**/** (**)	**/** (**)	
interval from last platinum based chemotherapy			
≤ 6 M	**/** (**)	**/** (**)	0.**
> 6M	**/** (**)	**/** (**)	

Table 20: Cochran Mantel Haenszel and Logistic Regression Model for best response rate

Data set: All Randomized Patients

	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factc	Odds Ratio (95%CI)	CMH p-vlaue	Odds Ratio (95% C.I.	p-value from logisti regression
Treatment arm		0.***		0.***
NAB-PACLITAXEL : *Paclitaxel*	**.** (**.**,**.*		**.** (**.**,**.*	
Prognostic factor 1		0.***		0.***
Level 1: level 2	NC [3]		**.** (**.**,**.*	
Prognostic factor 2		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
Prognostic factor 3		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
…		0.***		0.***
...	NC		**.** (**.**,**.*	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 21: Response rate According to Baseline Stratification Factors

	Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)		
	Nab-Paclitaxel N=***	*Paclitaxel* N=***	*Int-P-value*
ECOG performance status			0.**
0+1	**/** (**)	**/** (**)	
2+	**/** (**)	**/** (**)	
liver metastases			
Yes	**/** (**)	**/** (**)	0.**
No	**/** (**)	**/** (**)	
lymph node metastases only			
Yes	**/** (**)	**/** (**)	0.**
No	**/** (**)	**/** (**)	
hemoglobin			
< 100	**/** (**)	**/** (**)	0.**
≥ 100	**/** (**)	**/** (**)	
interval from last platinum based chemotherapy			
≤6 M	**/** (**)	**/** (**)	0.**
> 6M	**/** (**)	**/** (**)	

Table 21: Time to response

	Data set: All Randomized Patients		
	Univariate Analysis[1]		
Treatment Arm	Median TTR (Months) (95% CI)	Hazard Ratio[4] (95% CI)	Log-rank p-vlaue
Treatment arm			†0.***
NAB-PACLITAXEL	**.** (**.**,**.**)	**.** (**.**,**.**)	
Paclitaxel	**.** (**.**,**.**)		

Table 22: Duration of Response

Data set: All Randomized Patients with a Response of CR or PR				
	NAB-PACLITAXEL		Paclitaxel	
	N	Median (months) (95% CI)	N	Median (months) (95% CI)
Duration of Overall response (CR+PR)	***	**.** (**.**, **.**)	***	**.** (**.**, **.**)
Duration of Complete response (CR)	***	**.** (**.**, **.**)	***	**.** (**.**, **.**)

NOTE: Same table to be made based on all response evaluable patients

Table 23: Total treatment Duration and dose of Nab-Paclitaxel /Paclitaxel

Data Set: All Treated Patients		
Treatment arm Drug	NAB-PACLITAXEL	Paclitaxel
Duration in weeks:		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Mean (STD)	**(**)	**(**)
Total dose:		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Mean (STD)	**(**)	**(**)
Dose intensity		
Median	***	***
Mean (STD)	*** (**)	***(**)
Min – Max	***-***	***-***
Relative dose intensity		
Median	***	***
Mean (STD)	***(**)	***(**)
Min – Max	***-***	***-***
≥ 90% (n and %)	** (**)	** (**)
80%-90% (n and %)	** (**)	** (**)
<80% (n and %)	** (**)	** (**)

Table 24 : Dose Reduction, Interruption or Discontinuation

Data Set: All Treated Patients

	Number of patients (%)	
	Nab-Paclitaxel (N=***)	Paclitaxel (N=***)
At least one dose reduction, interruption or discontinuation	** (**)	** (**)
Reason for dose reduction, interruption or discontinuation:		
<*reason 1*>	** (**)	** (**)
<*reason 2*>	** (**)	** (**)
...	** (**)	** (**)
At least one dose reduction	** (**)	** (**)
Reason for dose reduction:		
<*reason 1*>	** (**)	** (**)
<*reason 2*>	** (**)	** (**)
...	** (**)	** (**)
At least one dose interruption	** (**)	** (**)
Reason for dose interruption:		
<*reason 1*>	** (**)	** (**)
<*reason 2*>	** (**)	** (**)
...	** (**)	** (**)
Protocol treatment discontinuation	** (**)	** (**)
Reason for discontinuation:		
<*reason 1*>	** (**)	** (**)
<*reason 2*>	** (**)	** (**)
...	** (**)	** (**)

Table 25: Hematology: Worst Ever Grade per Patient on Study

Data set: All Treated Patients		
	Number of patients (%)	
	NAB-PACLITAXEL	Paclitaxel
WBC		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Platelets		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Neutrophils		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Anemia		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Similar tables for Toxicities occurred at each cycle for the first 4 cycle of treatment.

Table 26: Biochemistry: Worst Grade per Patient over Study

Data set: All Treated Patients		
	Number of patients (%)	
	NAB-PACLITAXEL	Paclitaxel
ALT (SGPT)		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Total bilirubin		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Creatinine		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

(2) Greater than upper normal limit

NOTE: Patients can have more than one category (low and/or high)

Table 27: Toxicity/Adverse Events/Intercurrent Illness (worst ever over the study)

Data set: All Treated Patients (NAB-PACLITAXEL Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any AE	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE within category						
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category.

NOTE: In Paclitaxel Arm, the same type of table will be made. **Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both** NAB-PACLITAXEL **and Paclitaxel arms.**

Table 28: Worst Ever Toxicities/Adverse Event/Intercurrent Illness which are Serious, Fatal Only, Leading to Hospitalization

Data set: All Treated Patients (NAB-PACLITAXEL Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with serious AE within category						
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with fatal AE within categ						
Category 1[(1)]						
Event 1						
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1						
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with AE leading to hospitalization within category	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category.

NOTE: In Paclitaxel Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both NAB-PACLITAXEL and Paclitaxel arms.

Table 29: Worst Ever Toxicity/Adverse Event/Intercurrent Illness Led to Dose Discontinuation

Data set: All Treated Patients (**NAB-PACLITAXEL** Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any AE led to dos discontinuation	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE led to dose discontinuation within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

(1) Patients may have more than one event within a category.

NOTE: In Paclitaxel Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both NAB-PACLITAXEL and Paclitaxel arms.

Table 30: Worst Ever Toxicity/Adverse Event/Intercurrent Illness Led to Dose Interruption

Data set: All Treated Patients (**NAB-PACLITAXEL** Arm)

	Number of patients (%) N=***					
	Worst grade					Any gra
	NR	1	2	3	4	
Patients with any AE led to d interruption	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE led to dose interruption within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

(1) Patients may have more than one event within a category.

NOTE: In Paclitaxel Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both NAB-PACLITAXEL and Paclitaxel arms.

Table 31: Worst Ever Toxicity/Adverse Event/Intercurrent Illness Led to Dose Reduction

Data set: All Treated Patients (**NAB-PACLITAXEL** Arm)

	Number of patients (%) N=***					
	Worst grade					Any gra
	NR	1	2	3	4	
Patients with any AE led to dose reduction	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE led to dose reduc within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

(1) Patients may have more than one event within a category.

NOTE: In Paclitaxel Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both NAB-PACLITAXEL and Paclitaxel arms.

Table 32: Deaths on Study within 30 Days

Data set: All Treated Patients

	Number of Patients (%)	
	Nab- Paclitaxel N=***	Paclitaxel N=***
Number of Patients who died within 30 days of last treatment	** (**)	** (**)
Cause of Death		
Urothelial carcinoma (UC)	**	**
Toxicity from protocol treatment	**	**
UC + Toxicity from Protocol Treatment complication	**	**
Non-protocol Treatment Complication	**	**
UC + Non-protocol Treatment Complication	**	**
Other Primary Malignancy	**	**
Other Condition or Circumstance	**	**

Table 33: Summary of Supportive and Concomitant Medications and Therapy, Transfusion and hospitalization

Data Set: All Treated Patients						
	Number of patients (%)					
	Nab-Paclitaxel (n = ***)		Paclitaxel (n = ***)		TOTAL (n = ***)	
Any Antiemetics	***	(**)	***	(**)	***	(**)
Any Growth Factors & blood transfusion	***	(**)	***	(**)	***	(**)
Any Bisphosphonates and Bone Targeted Agents	***	(**)	***	(**)	***	(**)
Any hospitalization	***	(**)	***	(**)	***	(**)
Days of hospitalization	**		**		**	
Median	**-**		**-**		**-**	
Range						

* Patients may have received more than one type of concomitant medication

Table 34: Reason Off-protocol Therapy

	Number of patients (%)					
	NAB-PACLITAXEL (n = ***)		Paclitaxel (n = ***)		TOTAL (n = ***)	
Number (%) patients off study	**	(**)	**	(**)	**	(**)
Reasons off study						
Progressive disease	**	(**)	**	(**)	**	(**)
Symptomatic progression	**	(**)	**	(**)	**	(**)
Intercurrent disease	**	(**)	**	(**)	**	(**)
Toxicity to protocol treatment	**	(**)	**	(**)	**	(**)
Death	**	(**)	**	(**)	**	(**)
Other	**	(**)	**	(**)	**	(**)
Unknown	**	(**)	**	(**)	**	(**)
Patient refusal	**	(**)	**	(**)	**	(**)

Table 35: Compliance (Received/Expected) with QOL Assessment by Treatment Arm

	NAB-PACLITAXEL		Paclitaxel	
Period	Expected	Received (%)	Expected	Received (%)
Baseline	***	*** (**.*)	***	*** (**.*)
Cycle1	***	*** (**.*)	***	*** (**.*)
Cycle2	***	*** (**.*)	***	*** (**.*)
…	***	*** (**.*)	***	*** (**.*)
At progression	***	*** (**.*)	***	*** (**.*)
6 week FU 1	***	*** (**.*)	***	*** (**.*)
6 week FU 2	***	*** (**.*)	***	*** (**.*)
…	***	*** (**.*)	***	*** (**.*)

Table 36: Baseline Score for Each Domain/item

Domain/item		NAB-PACLITAXEL	Paclitaxel
Physical	N	***	***
	MEAN	**.**	**.**
	STD DEV	**.**	**.**
Emotional	N	***	***
	MEAN	**.**	**.**
	STD DEV	**.**	**.**
…	N	***	***
	MEAN	**.**	**.**
	STD DEV	**.**	**.**

Table 37: Mean QOL Change Scores from Baseline for each Domain/item at Each Assessment Time

	NAB-PACLITAXEL		Paclitaxel		
Assessment	N	Mean (SD)	N	Mean (SD)	P value*
Cycle1	***	**.** (**.**)	***	**.** (**.**)	0.**
Cycle2	***	**.** (**.**)	***	**.** (**.**)	0.**
…	***	**.** (**.**)	***	**.** (**.**)	0.**
Progression	***	**.** (**.**)	***	**.** (**.**)	0.**
6 week FU 1	***	**.** (**.**)	***	**.** (**.**)	0.**
6 week FU 2	***	**.** (**.**)	***	**.** (**.**)	0.**
…….					

*Wilcoxon rank sum test.

(There will be one table for each domain/item).

Table 38: Results for QOL Response Analyses

Domain	Nab- Paclitaxel			Paclitaxel			P-value (Chi-square test)	p-value (MH trend test)
	Improved N (%)	Stable N (%)	Worsen N (%)	Improved N (%)	Stable N (%)	Worsen N (%)		
EORTC QLQ-C15-PAL								
Physical	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Emotional	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Global	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Pain	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Fatigue	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Nausea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Insomnia	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Appetite	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
Constipation	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**
FACT-Taxane								
	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**