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NCIC CLINICAL TRIALS GROUP (NCIC CTG)

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

NCIC CTG Protocol Number: **BL.12**

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Celgene.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by NCIC CTG and Celgene to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Celgene and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Celgene and NCIC CTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to NCIC CTG. The study may be terminated at any time by NCIC CTG or Celgene with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Celgene and NCIC CTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: NCIC CTG BL.12

CENTRE: _____

TREATMENT SCHEMA

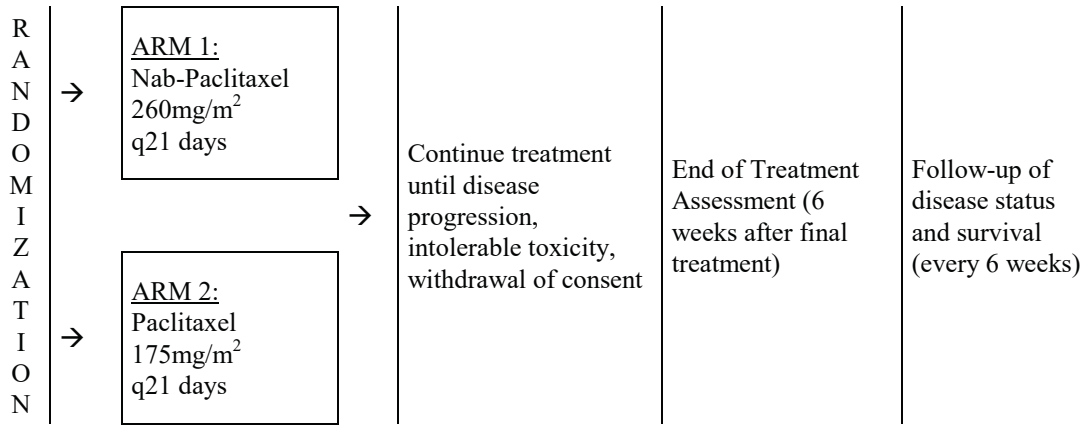
This is an international multi-centre, open-label, randomized phase II trial comparing nab-paclitaxel to paclitaxel in patients with advanced urothelial cancer progressing on or after a platinum-containing regimen.

Population:

- Patients with metastatic or locally advanced inoperable urothelial cancer
- ECOG performance status 0-2
- Progression on or ≤ 1yr of platinum based chemotherapy
- No prior taxanes

Stratification:

- Centre
- ECOG performance status (0, 1 versus 2)
- Liver metastases (yes versus no)
- Lymph node metastases only (yes versus no)
- Hemoglobin (< 100 g/L versus ≥ 100 g/L)
- Interval from last platinum based chemotherapy (≤ 6 months versus > 6 months)



1 Cycle = 21 days
N = 199 patients

1.0 OBJECTIVES

1.1 Primary Objective

- To compare progression free survival (PFS) between the two arms.

1.2 Secondary Objectives

- To compare overall survival (OS) between arms.
- To compare objective response rates (complete or partial response (ORR)) between arms.
- To compare clinical benefit rate (CBR), as determined by 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 (SD) for at least 12 weeks (ORR+SD $\geq$ 12 weeks) between arms (all patients - with or without measurable disease at baseline).
- To estimate time to response and response duration.
- To evaluate and compare the nature, severity, and frequency of toxicities, including neuropathy between the two arms.
- To compare the quality of life between the two arms.
- To determine the incremental cost effectiveness and cost utility ratios for nab-paclitaxel versus paclitaxel.

1.3 Exploratory Objectives

- To correlate the expression of tissue markers (at diagnosis) with outcomes and response in an exploratory fashion.
- To assess genetic polymorphisms that may impact on response or toxicity to the taxanes.
- To assess the effect modification of and adjust for clinico-demographic factors captured in a health and demographic questionnaire with respect to the relationships between biomarkers, quality of life, health economics, disease outcomes, and treatment toxicities.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Urothelial Cancer

Urothelial carcinoma (UC) is a major oncologic problem and fifth most commonly diagnosed cancer in Canada with approximately 7,900 new cases and 2,100 deaths occurring annually *[Canadian Cancer Society Statistics, 2013].* Worldwide estimates suggest there are about 400,000 new cases and 150,000 deaths annually, representing a significant burden on the healthcare system. The majority of UC are transitional cell carcinomas (TCC) and occur in males. Although the most common presentation of UC is non-muscle invasive disease, many patients will present with or develop muscle invasive disease (MIUC), where despite multimodality treatment, up to 50% of these patients will develop metastatic disease. Metastatic UC is a chemosensitive disease and the two most commonly used regimens in the first line setting are gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Although initial response rates to cisplatin-based chemotherapy in the metastatic setting are high, disease progression is common and overall survival is a dismal 15 months *[von der Maase 2000, von der Maase 2005],* resulting in a growing number of patients in need of effective second-line chemotherapy. For this population there is currently no standard of care, underscoring the need for novel treatment approaches.

2.2 Current Second Line Therapies in Urothelial Cancer

Many agents, as shown in Table 1, have shown single agent response rates between 10-20%, but these responses are short lived with a median duration of only about 2 months. No randomized trials have shown a benefit of one regimen over another. In Europe, vinflunine, a microtubule targeting vinca alkaloid has gained approval in the second-line setting but the clinical benefit is modest. In the registration phase III trial of vinflunine versus best supportive care, in patients progressing after a first-line platinum regimen, vinflunine had a median survival of 6.9 months vs. 4.6 months for best supportive care, but this was not statistically significant. (p=0.287) *[Bellmunt 2009]*. Pemetrexed, an antifolate agent, has also shown reasonable response rates in this setting *[Sweeney 2006]*. Toxicity however remains a major concern in the second line setting because patients often have poor performance status and renal function. As a result, and with the lack of any proven options, the taxanes have become a commonly used second line treatment standard. Median survival with paclitaxel and docetaxel are in the 6 month range in phase II trials, underscoring the need for novel therapeutic approaches.

Table 1: Single agent studies in second line urothelial cancer

Author	Agent	Evaluable patients	Overall response rate	Median TTP months	Median survival months
Vaughn[2002]	Paclitaxel	31	10%	2.2	7.2
McCaffrey[1997]	Docetaxel	20	13%	-	9
Witte[1997]	Ifosfamide	56	20%	2.5	5.5
Lorusso[1998]	Gemcitabine	35	23%	3.8	5
Bellmunt[2009]	Vinflunine	370	9%	3.0	6.9
Sweeney[2006]	Pemetrexed	47	28%	2.9	9.6

2.3 Nab - Paclitaxel

To date, the highest single agent, second line response rates have been reported with an albumin-bound nanoparticle formulation of paclitaxel, known as nab-paclitaxel (Nab-paclitaxel®). Nab-paclitaxel is an IV chemotherapy that is currently approved for the management of metastatic breast cancer and is FDA approved for use in combination with carboplatin for metastatic non-small cell lung cancer. In a multi-institutional phase II study of 47 metastatic UC patients progressing on or after a first line platinum based regimen, nab-paclitaxel was well tolerated and showed an objective response rate of 28% and a clinical benefit rate of 49%. The progression free survival was 6 months and overall survival was 10.8 months *[Ko 2013]*. These results provide the basis for this randomized phase II clinical trial, which is designed to confirm that nab-paclitaxel can slow tumour progression and enhance survival outcomes compared with standard paclitaxel. In addition, nab-paclitaxel may be better tolerated because it does not require steroid premedication and has an altered toxicity profile compared to paclitaxel and docetaxel

Dose Considerations
Based on the encouraging results from the phase II study *[Ko 2013]* and the limited toxicity of nab-paclitaxel at a dose of 260mg/m^2 administered every 3 weeks, this dose and schedule was chosen to take forward into the randomized phase II setting. The other benefit of q3wkly dosing is that in this relatively older and more frail second line UC population, weekly visits for treatment may be burdensome.

Paclitaxel single agent given every 3 weeks was chosen as the comparator arm for several reasons. First, it will allow a direct comparison of efficacy and tolerability between nab-paclitaxel and standard paclitaxel in this patient population. This is similar to the design used by Gradishar et al, in the metastatic breast cancer phase III trial *[Gradishar 2005]*. Paclitaxel has been relatively well studied in this disease, both in first line (RR=20%) and in second line (RR=10%) settings. Paclitaxel is also commonly used in the second line setting, which will assist with study participation, interpretation and applicability of study results.

2.4 Correlative Studies

It is hypothesized that the expression of molecular markers may correlate with outcomes and response to therapy. If this proves to be the case, it may be feasible to attempt to better define a cohort of patients who are most suitable for a therapy. All patients randomized to the trial, who consent to submission of tissue, will have tissue collected as paraffin embedded blocks. In addition, blood samples will also collected for all consenting patients.

2.4.1 *Biomarkers of Interest*

Formalin Fixed Paraffin Embedded (FFPE) Specimens:
Recently, sensitivity to anti-tubulin chemotherapy drugs such as paclitaxel was found to be regulated by MCL1 and FBW7 proteins in cell lines and primary cancer tissues *[Wertz 2011]*. MCL1 inhibits apoptosis by blocking the cell death mediators, BAX and BAK. MCL1 contains potential degron motifs for association with F-box proteins FBXW1 and FBW7. F-box proteins are substrate receptors for ubiquitin ligase complexes. Thus, gene and protein expression may be associated with response to paclitaxel. MCL1 and FBW7 will be determined by reverse transcription polymerase chain reaction (RT-PCR). It has also been shown that expression of microtubule associated proteins, total tau (cytoplasmic and nuclear) and strathmin in non-muscle invasive bladder cancer before intravesical taxane therapy may predict for response to therapy. Tumours with low tau/strathmin expression had shown better response to therapy. Expression of these two microtubule associated proteins can be determined by immunohistochemistry (IHC) on FFPE specimens *[Wosnitzer 2011]*.

Another biomarker of interest relates to SPARC (secreted protein acidic and rich in cysteine). SPARC expression in UC is associated with higher grade and worse prognosis. SPARC interacts with albumin and may promote the accumulation of albumin in the tumour thus increasing the effectiveness of nab-paclitaxel *[Yamanaka 2001]*.

2.4.2 *DNA-Based Germline Genetic Sequence Variants*

It will also be important to determine if genetic polymorphisms, specifically in the genes CYP2C8, NR1/2, ABCB1, EPHA5, FGD4, and NRDG1 impacts on disease outcome and toxicity. In addition, a health and demographic questionnaire will be incorporated into the study design that will ask about social habits, family history, and other relevant clinico-demographic factors. An exploratory hypothesis will assess whether there is an association of the aforementioned markers with the factors being assessed in the questionnaire.

The systemic elimination of paclitaxel involves CYP3A4 and CYP2C8. Paclitaxel is converted to 3′-p-hydroxypaclitaxel by CYP3A4, while CYP2C8 catalyzes the formation of 6α-hydroxypaclitaxel. Several single nucleotide polymorphisms (SNPs) have been reported in *CYP2C8* and some variant alleles have been associated with a reduced 6α-hydroxypaclitaxel production *in vitro*. However, the effects of *CYP2C8* polymorphisms on paclitaxel pharmacokinetics or pharmacodynamics in patients are still unclear and recent reports seem to scale down the significance of CYP2C8 polymorphisms (PMID: 19761371). CYP3A4 expression is known to be regulated by the pregnane/steroid X receptor (PXR), coded by the NR1I2 gene. PXR is a well established regulator of many other genes including *CYP3A5, CYP2C8* and *ABCB1*. Polymorphisms in the NR1I2 gene have been reported to modulate CYP3A4 expression (PMID: 17050801), although their clinical effect remains to be elucidated. Paclitaxel is a substrate of P-gp which reduced activity increases the cell sensitivity to the drug by an ineffective P-gp efflux. A reduced P-gp mediated transport from blood to intestine would increase systemic drug exposure, affecting paclitaxel pharmacokinetics. Moreover, cancer cells with an ineffective P-gp efflux should be more sensitive to the drug. P-gp is encoded by the ATP Binding Cassette gene (*ABCB1*). Among at least 50 common polymorphisms described in ABCB1 gene in Caucasians, *2677G>T/A (Ala893Ser/Thr)* and *3435C>T* polymorphisms have been shown to correlate with the P-gp expression and phenotype. The mechanism underneath the association of *ABCB1-2677G>T/A* polymorphism with toxicity and efficacy seem related to an effect on the pharmacokinetics: the presence of the *2677T/A* allele affects the paclitaxel clearance, that resulted lowered in patients carrying the variant allele *[Green 2008]*. In addition to this data, pathway polymorphism signatures of efficacy and toxicity (based on genome-wide association studies) of combination drug regimens involving paclitaxel are being developed in NCIC CTG BR.24 (PI G Liu), and ICON7 (co-PIs H. Mackay and G. Liu). A genome-wide association analyses was recently completed of CALGB 40101, a phase III randomized study of adjuvant cyclophosphamide and doxorubicin versus single-agent paclitaxel in women with operable breast cancer and 0-3 positive axillary lymph nodes. There were approximately 900 patients treated in the paclitaxel arm. A polymorphic signature has been developed that is associated with dose-to-toxicity outcomes.

2.5 Health and Demographic Questionnaire (HDQ)

A Health and Demographic Questionnaire will be administered for multiple hypotheses. First, certain risk factors may be related to different biological carcinogenic processes, and the resultant biological differences may have prognostic and/or predictive implications (Hypothesis A). Secondly, risk factor, lifestyle, and other demographic factors may be important as confounders or effect modifiers of correlative science hypotheses (described above) (Hypothesis B). In addition these risk factors may impact quality of life, and health economic analyses, efficacy, and disease outcome (Hypothesis C). Finally, information derived will help us understand the generalizability of data in the non-trial setting. Clinical trials tend to have a selection bias for healthier, lower-comorbidity, urban patients compared to the general population but our ability to quantify this level of selection bias has been limited in the past (Hypothesis D).

The table below summarizes the planned use of data collected on the HDQ, the hypotheses described above, the sources of questions in each category, and pre-specified summary scores involving reclassification of primary questionnaire data for analysis. The following are five illustrative but not exhaustive examples derived from the table below that outlines the rationale for use of this HDQ information in our pre-specific analyses:

i) Body Mass Index (BMI) has been linked with level of neurotoxicity of paclitaxel-treated patients. It will serve as an adjustment covariate for the toxicity analysis of 2.4.2 (Hypothesis A), as an effect modifier for this toxicity (Hypothesis B), and to determine role of BMI directly with disease outcome (ghrelin/IGF hypothesis and cancer prognosis; Hypothesis C).

ii) Occupational history may define a subgroup of patients sicker or with biologically heterogeneous bladder cancer (Hypothesis A), or to better understand the distribution of this trial population against epidemiological studies of this disease (Hypothesis D).

iii) In Section 2.4.2, we will assess germline genetic factors. The relationship between family history of cancer and genetic factors is explored as potential effect modifiers of each other (Hypotheses A and B).

iv) Smoking, alcohol use, and/or physical activity are known risk factors for cancer and in some studies, bladder cancer (Hypothesis A). These same factors may confound or be effect modifiers of disease outcome (Hypothesis B), or be independent predictors of treatment effect (Hypothesis C). Understanding the distribution of these factors will improve our understanding of the typical bladder cancer patient in this trial, when compared to the wider non-trial population (Hypothesis D), which is important in trial generalizability and in any pharmacoeconomic analyses. Such variables may also be important as potential confounders or effect modifiers of QoL and pharmacoeconomic analyses (Hypothesis B).

v) Neurotoxicity is thought to be differentially perceived by gender, which has led some to speculate about hormonal involvement in symptom perception. The candidate polymorphisms chosen in Section 2.4.2 are derived from breast cancer studies involving women and thus it may be useful to investigate the potential confounding effects of hormonal elements vis-à-vis hormonal elements in altering neurotoxicity and QoL outcomes.

Table 2: HDQ Components, Rationale for Use, and Sources of Questions.

Category	**Source(s) of questions in this category**	**Summary Scoring Source**	**Hypothesis (A, B, C, D as above)**
Background Information	HECS* US and Canadian Census Categories (Ethnicity)	Body Mass Index (standard)	(A), (B), (C) (D)
Occupational History	HECS		(A), (D)
Family History	HECS	First degree Y/N	(A), (B), (D)
Smoking	American Thoracic Society Survey; HECS	Pack-years	(A), (B), (C), (D)
Alcohol	HECS	Drink-years	(A), (B), (C), (D)
Physical Activity	Adapted from CALGB 89803	PMID:24035029	(A), (B), (C), (D)
Women's History	HECS and Terry Fox Research Institute Pan-Canadian Lung Cancer Screening Study	Cumulative Estrogen Exposure	(A), (B) with correlative questions associated with DNA sequence variants (2.4.2)
HECS* Harvard Epidemiologic Cancer Study: PMID:11888908, PMID:21212151, PMID:18559624			

2.6 Quality of Life

As described above, patients requiring second-line chemotherapy for advanced bladder cancer have a limited life expectancy. The impact of a new intervention, compared to conventional management, must consider both the relative effectiveness of palliating symptoms of disease, and the relative toxicities of each intervention. The former is determined by assessing improvement in those baseline quality of life (QoL) scores that reflect the impact of metastatic disease, and the latter are determined by assessing new adverse Health-Related Quality of Life (HRQL) scores that develop on treatment. For patients enrolled on BL12, the baseline HRQL scores at randomization may also reflect the toxicities of first-line chemotherapy, further complicating the analyses and interpretation of HRQL data collected on BL.12.

As detailed in section 3.1.10 below, treatment-related toxicity attributed to nab-paclitaxel may differ from that associated with paclitaxel. Specifically, nab-paclitaxel does not require steroid administration (and avoids steroid-related impact on QoL such as insomnia, restlessness and sequelae of hyperglycemia), has a shorter infusion time, is likely to have less severe neuropathy with faster recovery time, and less hypersensitivity.

The key QoL specific hypotheses in this trial are as follows:

a. Nab-paclitaxel will be more effective at controlling metastatic disease; this treatment benefit will manifest in higher rates of response in QoL domain scores relevant to disease burden (e.g. physical function, pain) after two cycles of treatment.

General QoL domains will be assessed using the EORTC-C15-PAL questionnaire *[Groenvold 2006]*. This self-administered questionnaire is a shortened version of widely used EORTC-QLQ-C30 *[Aaronson 1993]*. 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. The data will contribute to the NCIC CTG experience with the use of the QLQ-C30 in comparable settings of second-line or third-line chemotherapy *[Osoba(b) 2005, Osoba(a) 1996]*.

The efficacy of each respective treatment arm with regard to QoL benefits will be tested using between group comparisons including: between-arm change in mean domain scores; and a difference in proportion of patients with a minimum clinically important improved change score (10 points on the EORTC 100-point transformed domain scores) *[Osoba(a) 1996]*.

b. Patients randomized to nab-paclitaxel will have less treatment-related toxicity, which will manifest as fewer adverse changes in short-term QoL scores in relevant domains.

Early treatment related toxicity will be evaluated shortly after treatment administration. Since the instrument has a recall period of 7 days, administration will occur 5-7 days after treatment. Short term adverse effects of treatment (nab-paclitaxel, paclitaxel, and steroid pre-medication) noted above will be assessed by several domains of the EORTC instrument including nausea and vomiting, fatigue, insomnia, bowel symptoms, social and cognitive functioning, among others. Between group comparisons will include both: between-arm change in mean domain scores; and a difference in proportion of patients with a minimum clinically important negative change score (10 points on the EORTC 100-point transformed domain scores *[Osoba(a) 1996]*.

c. Patients randomized to nab-paclitaxel will have less severe treatment-related peripheral neuropathy, which will also be of shorter average duration, compared to patients randomized to paclitaxel.

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 will be important to detect. For this purpose, the FACT-Taxane questionnaire will be 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 *[Cella 2003]*.

2.7 Health Economics

The experimental arm of nab-paclitaxel is not only hypothesized to provide better efficacy for survival but also advantages with regards to ease of administration and reduced toxicities. The purpose of the economic evaluation is to determine the incremental cost-effectiveness and cost-utility of nab-paclitaxel. The perspective will be a universal public payer. Outcomes of interest will include: incremental costs, life years (LY) gained, quality adjusted life years (QALY) gained between comparators. From this data, Incremental cost/LY (Dollars/LY) and cost/QALY (Dollars/QALY) ratio will be calculated.

Utility weights will be collected prospectively during the trial using the EQ-5D Questionnaire administered to patients in both arms of the study. Resource utilization will be limited to direct medical costs. Resource use solely related to research, and not patient care as it would be given outside of a clinical trial, will be excluded. Costs will be discounted 5% annually in the base case beyond a one year time horizon. A mean overall treatment cost per patient will be derived for each treatment arm.

Markov modeling will only be used, if at all, for any important elements found to be missing from the study database or if there is a need to extrapolate beyond the clinical trial time horizon. The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted.

In summary, BL.12 is a randomized phase II study that will provide important data regarding the efficacy, tolerability, QoL and economic impact of use of nab-paclitaxel compared to paclitaxel as second line therapy for metastatic UC. In addition, biospecimen collection and analysis will provide information regarding predictive and prognostic factors for use of taxanes in this patient population.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Nab-Paclitaxel

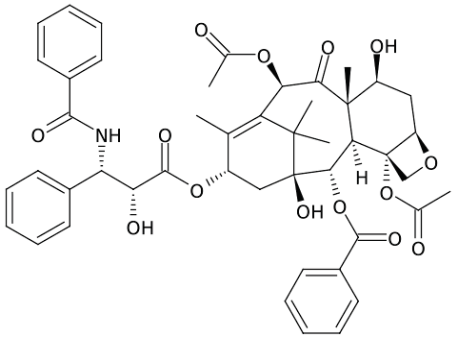
3.1.1 *Name and Chemical Information*

Nab-Paclitaxel (Abraxane®) is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Each 50 mL vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection.

Chemical name (IUPAC): (2α,4α,5β,7β,10β,13α)-4,10-bis(acetyloxy)-13-{[(2R,3S)- 3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy)- 1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate

3.1.2 *Chemical Structure*

Structural formula:



Molecular formula: $C_{47}H_{51}NO_{14}$
Molecular weight: 853.91

3.1.3 *Mechanism of Action*

Nab-paclitaxel is a novel, nanometer-sized albumin-bound paclitaxel particle initially developed to avoid the toxicities associated with polyethylated castor oil, used in standard taxanes. It is the first of a new class of agents that use albumin particle technology and exploits the unique properties of albumin a natural carrier of lipophilic molecules in humans. This technology provides a novel approach for increasing intra-tumoural concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell.

This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intraluminal endothelial cell membrane, resulting in activation of a protein (caveolin-1). Caveolin-1 initiates an internalization process in the endothelial cell through the formation of caveolae, which transport the intact albumin-bound paclitaxel complex via these caveolae to the underlying tumour interstitium [Desai 2009]. The drug albumin complex, then binds to a protein secreted by a number of tumours including urothelial cancers, known as secreted protein acidic and rich in cysteine or SPARC. SPARC binds to albumin and then allows the release of the hydrophobic drug at the tumour cell membrane *[Desai 2009]*. Nab-paclitaxel is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway in order to increase intra-tumoural concentrations of paclitaxel and reducing toxic effects in normal tissue.

3.1.4 *Experimental Antitumour Activity*

A range of preclinical studies in the appropriate species have been completed with nab-paclitaxel including single and repeat-dose toxicity studies, carcinogenicity evaluations, reproductive toxicity assessments, and mutagenicity and toxicity studies. A thorough discussion of these is included in the Investigator's Brochure (IB). Preclinical studies comparing nab-paclitaxel to paclitaxel (Taxol® paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with a maximum tolerated dose (MTD) approximately 50% higher for nab-paclitaxel compared to paclitaxel. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumour model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, nab-paclitaxel treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumour paclitaxel area under the curve was 33% higher for nab-paclitaxel versus solvent based paclitaxel, indicating more effective intratumoural accumulation of nab-paclitaxel *[Desai 2008]*.

3.1.5 *Animal Toxicology*

Single-dose studies showed that nab-paclitaxel is well tolerated in rats and mice. Lethal doses (LD50 and LD10) were notably higher for animals treated with nab-paclitaxel than for those treated with solvent-based paclitaxel. Nab-paclitaxel produced less myelosuppression in rats than solvent based paclitaxel (WBC nadir of 24% and 55% below baseline, respectively). Furthermore, the recovery periods from WBC suppression were about 7 days and 14 days for the nab-paclitaxel and solvent-based paclitaxel-treated animals, respectively. The vehicle for solvent based paclitaxel produced neutropenia, which was similar in extent (~61% below baseline) and recovery period to solvent-based paclitaxel-induced neutropenia. Thus, the vehicle for solvent-based paclitaxel contributed substantially to the reduction in WBC count. In contrast, the nab-paclitaxel vehicle showed no significant myelosuppression. Cortical necrosis was observed in solvent-based paclitaxel-treated rats, whereas no evidence of this central nervous system damage was observed in rats that received doses of nab-paclitaxel up to 120 mg/kg. Nab-paclitaxel caused necrosis and diffuse degeneration in male reproductive organs; little remarkable female toxicity was observed, and no notable damage to reproductive organs was found. Mortality was low for nab-paclitaxel (1/60 for all dose groups) but significant for solvent-based paclitaxel (12/12 at 30 mg/kg). Acute toxicity studies in dogs and swine provided limited information due to the development of serum sickness secondary to the human albumin contained in the formulation.

3.1.6 *Phase I Trials*

In a phase I study, the MTD of nab-paclitaxel was determined to be 300 mg/m^2 by 30 minute infusion Q3W, without premedication or G-CSF support *[Ibrahim 2002]*. No severe hypersensitivity reactions occurred with nab-paclitaxel despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2.

3.1.7 *Phase II Trials*

In patients with metastatic breast cancer, two multicentre phase II studies have evaluated 2 dose levels of nab-paclitaxel (175 mg/m^2, n=43 and 300 mg/m^2, n=63) *[Ibrahim 2005]* and nab-paclitaxel (Investigator's Brochure), respectively. The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m2 dose, and 48% (95% CI 35-60%) for the 300 mg/m2 dose. Of 39 patients receiving 300 mg/m2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

3.1.8 *Phase III Trials*

A phase III trial in metastatic breast cancer compared nab-paclitaxel 260 mg/m^2 (n=229) to paclitaxel 175 mg/m^2 (n=225) given Q3W *[Gradishar 2005]*. The objective response rate (ORR) was significantly greater for nab-paclitaxel than for paclitaxel for all patients (33% v 19%, respectively; P = 0.001). Median time to progression (TTP) was also significantly longer with nab-paclitaxel than with paclitaxel (23.0 v 16.9 weeks, respectively; hazard ratio [HR] = 0.75; P = 0.006). In addition, there was a trend for greater median survival for all patients treated with nab-paclitaxel compared with paclitaxel (65.0 v 55.7 weeks, respectively; P = 0.374) *[Gradishar 2005]*. The incidence of hypersensitivity reactions (any grade) was low for both arms and no grade 3 or higher hypersensitivity reactions were seen.

In non-small cell lung cancer (NSCLC), a phase III trial of 1052 patients, has shown that nab-paclitaxel plus carboplatin had a higher ORR (35% vs. 27%) than paclitaxel plus carboplatin, with a trend towards improved PFS and OS. This phase III study has led to the recent FDA approval of nab-paclitaxel for use in combination with carboplatin in this setting *[Satouchi 2013]*.

In metastatic pancreatic cancer a phase III trial in 861 patients has shown that nab-paclitaxel 125 mg/m2 plus gemcitabine 1000mg/m2 every 3 weeks, improved survival by 2 months compared to gemcitabine alone (median, 8.5 vs. 6.7 mo; HR 0.72, P=0.000015) *[Tabernero 2013]*.

In metastatic melanoma, a phase III trial comparing nab-paclitaxel to dacarbazine, has demonstrated improved median OS (8.5 vs. 6.7 HR 0.72, p=0.000015), and PFS (5.5 vs. 3.7, HR 0.69, p= 0.0000024) for patients receiving nab-paclitaxel *[von Hoff 2013]*.

In Canada and the US, nab-paclitaxel for Injectable Suspension is currently indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy; and has recently been approved by the Food and Drug Administration for use in metastatic NSCLC patients in combination with carboplatin and for the treatment of adenocarcinoma of the pancreas in combination with gemcitabine in first line treatment.

3.1.9 *Pharmacokinetic Studies*

Nab-paclitaxel is dissolved in saline for infusion. An initial phase I clinical trial showed that this drug is tolerated up to a maximum tolerated dose of 300 mg/m^2, administered as a 30-minute infusion, without any premedication. A subsequent phase II study using this dosing regimen required dose reductions in 25% of patients due to toxicity primarily neutropenia and neuropathy. Therefore, the phase III study that led to the Food and Drug Administration approval of nab-paclitaxel for treatment of metastatic breast cancer, used a dose of 260 mg/m^2 administered as a 30-minute infusion, and compared this with standard paclitaxel at a dose of 175 mg/m^2 given as a 3-hour infusion. This study showed significantly higher response rates and longer time to tumour progression in the group receiving nab-paclitaxel *[Gradishar 2005]*.

Six completed studies in the clinical program examined the PK parameters of nab-paclitaxel in humans: five Phase I studies (DM97-123 [dose-ranging, q3w regimen], CA005 [dose ranging, weekly regimen], CA008 [single-dose comparison with solvent-based paclitaxel], CA019 [randomized, crossover study with nab-paclitaxel and solvent-based paclitaxel], CA037 [safety and PK of nab-paclitaxel in patients with hepatic dysfunction]) and 1 sub study of a phase III trial (CA012) *[Sparreboom 1998]*. Key parameters for the phase III trial are presented in Table 3.

Table 3. Mean nab-paclitaxel PK Parameters in Humans in the Phase III Trial

Study No	Nab-paclitaxel Dose (mg/m^2)	Infusion Duration	n	C_{max} (ng/ml)	AUC0-inf (ng/mL·h)	$t_{1/2}$ (h)	CL (L/ h/m^2)
CA012	260	30	12	18,741	17940	27.4	15.2

PK = Pharmacokinetic; C_{max} = maximum (peak) concentration; AUC0-inf = area under the plasma concentration-time curve from time zero to infinity; $t_{1/2}$ = half-life; CL = total body clearance.

Paclitaxel pharmacokinetics in patients treated with nab-paclitaxel displayed a multi-phasic disposition and the non-compartmental parameters were in agreement with previously reported data. Total clearance (CL) had a mean value of 15.2 L/h/m^2, the half-life ($t_{1/2}$) was 27.4 hr, and the volume of distribution (Vz) was 632 L/m^2. Modest variability was found among individual patient parameters. The paclitaxel metabolites 6 alpha-hydroxypaclitaxel and 3'-phydroxypaclitaxelconcentration-time data in blood followed similar profiles to parent drug except that metabolite concentrations were substantially lower. Paclitaxel was the predominant species in blood and urine samples while 6ά-hydroxypaclitaxel was predominant in feces. Total dose recovery from urine and feces accounted for approximately 26% of the nab-paclitaxel dose, with feces being the major excretion route.

3.1.10 *Safety and Toxicity Data*

Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia are the most commonly reported toxicities. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

3.1.11 *Pharmaceutical Data*

Supplied:
ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) is supplied as a white to yellow, sterile, lyophilized cake for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Paclitaxel exists in the particle in a non-crystalline, amorphous state. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE® is free of solvents.

ABRAXANE® is available in a single-use glass vial with a latex free stopper, individually packaged in a carton.

Storage:
Store the vials of ABRAXANE® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab®] paclitaxel) in original cartons between 20 and 25°C. Retain in the original package to protect from bright light. Neither freezing nor refrigeration adversely affects the stability of the product.

Solution Preparation:
Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the inside wall of the vial. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

ABRAXANE® reconstituted in the original vial should be used immediately, but may be refrigerated between 2 and 8°C for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed.

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 20 to 25°C) and ambient lighting conditions for up to 8 hours.

Route of Administration:
Nab-Paclitaxel is administered intravenously as a colloidal suspension of 130 nm particles, a formulation that allows for higher doses of paclitaxel to be administered, than with the standard paclitaxel therapy, with shorter infusion schedules (30 minutes vs. 3 hours respectively) without the need for premedication.

See label/package insert for additional information.

3.2 Paclitaxel

3.2.1 *Background Drug Information*

Paclitaxel is a commercially available anticancer agent used in the management of ovarian and breast cancer. It acts at the cellular level as a promoter of microtubule assembly. Paclitaxel binds preferentially to microtubules, rather than the subunit tubulin dimers, thus stabilizing microtubules and inhibiting the normal dynamic reorganization of the microtubule network. These events culminate in cell death.

Paclitaxel's primary toxic effects include myelosuppression (mostly neutropenia), peripheral neuropathy, arthralgias and myalgias and hypersensitivity reactions. These latter are seldom severe when the drug is infused after appropriate premedication regimens. A series of phase II and subsequent phase III trials have established the efficacy of paclitaxel firstly as a single agent treatment for early and advanced disease and more recently as part of the frontline combination management of this disease.

In this trial commercial supply of paclitaxel will be used. See label/package insert for additional information.

4.0 TRIAL DESIGN

This is a multicentre, open-label, randomized phase II trial comparing nab-paclitaxel (nab-paclitaxel®) to paclitaxel in patients with advanced urothelial cancer progressing on or after a platinum-containing regimen.

4.1 Stratification

Patients will be stratified by:

- Centre
- ECOG performance status (0, 1 versus 2)
- Liver metastases (yes versus no)
- Lymph node metastases only (yes versus no)
- Hemoglobin (< 100 g/L versus ≥ 100 g/L)
- Interval from last platinum based chemotherapy (≤ 6 months versus > 6 months)

4.2 Randomization

Patients will be randomized to receive one of the following treatments: nab-paclitaxel or paclitaxel chemotherapy, to a planned sample size of 199. Patients will be receive treatment until disease progression, intolerable toxicity or withdrawal of consent.

Patients will be randomized to one of the following two arms:				
Arm	Agent(s)	Dose	Route	Duration
1	Nab-Paclitaxel	260 mg/m^2 Q21 days	IV	Until disease progression or unmanageable toxicity or withdrawal of consent
2	Paclitaxel	175 mg/m^2 Q21 days	IV	

5.0 STUDY POPULATION

This is an international multi-centre, open-labeled, randomized phase II trial comparing nab-paclitaxel (Nab-paclitaxel®) to paclitaxel in patients with advanced urothelial cancer progressing on or after a platinum-containing regimen

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically or cytologically confirmed diagnosis of TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) and metastatic or locally advanced inoperable disease extent (T4, N2, N3 or M1 disease) (See Appendix VII for TNM Staging).

Note: Mixed histologies (except small cell) permitted if predominantly TCC by IHC.

5.1.2 Patients must have evidence of metastatic disease, but measurable disease is not mandatory. To be considered evaluable for the overall response rate (complete and partial response), patients must have at least one measurable lesion as follows:

- X-ray, physical exam $\geq$ 20 mm
- Conventional CT scan, MRI $\geq$ 20 mm
- Spiral CT scan $\geq$ 10 mm

5.1.3 Male or female, 18 years of age or older.

5.1.4 ECOG performance status $\leq$ 2 at study entry (see Appendix II).

5.1.5 Adequate hematological, renal and hepatic functions as defined by the following required laboratory values obtained within 14 days prior to randomization. If anemic, patients should be asymptomatic and should not be decompensated.

- Absolute neutrophil count (ANC) $\geq$ 1.5 x10^9/L (1,500 cells/mm^3)
- Platelet count $\geq$ 90 x10^9/L (100,000/mm^3)
- Hemoglobin $\geq$ 90 g/L
- Calculated creatinine clearance > 25 mL/min (Cockcroft and Gault formula)

- Total bilirubin ≤ 1.5 times the upper limit of normal (≤ 2.5X if Gilbert's disease)
- ALT (SGPT) ≤ 3 x ULN or ≤ 5 x ULN if hepatic metastases are present

5.1.6 Patients may have had prior neoadjuvant or adjuvant therapy for completely resected disease, provided it was completed at least 12 months prior to randomization. Patients must have recovered from any acute toxic effects to ≤ Grade 2 from any prior treatments. Neoadjuvant or adjuvant chemotherapy will be considered to have been first line therapy in the metastatic setting if the patient progressed within 12 months of the last dose.

5.1.7 Patients must have received one and only one prior chemotherapeutic regimen which included a platinum (at least one cycle) for metastatic/recurrent disease. Treatment must have been discontinued at least 4 weeks prior to randomization in this study. Patients must have recovered from any acute toxic effects to ≤ Grade 2 from any prior treatments.

5.1.8 Patients may not have had any prior therapy with a taxane in any setting.

5.1.9 Patients may have had prior investigational agents but these must have been discontinued at least 4 weeks prior to randomization. Patients must have recovered from any acute toxic effects to ≤ Grade 2 from any prior treatments.

5.1.10 Prior treatments with radiation therapy in the adjuvant and/or metastatic setting are permitted provided that at least 2 weeks have elapsed since the last fraction of radiation therapy and all treatment related adverse events are ≤ Grade 1 at the time of randomization.

5.1.11 Patients may have had prior surgery provided that at least 4 weeks elapsed between the end of surgery and randomization onto the study. Patients must have recovered from any acute toxic effects to ≤ Grade 2 from any prior treatments.

5.1.12 Patients may have peripheral neuropathy from previous treatments provided that it is ≤ Grade 1.

5.1.13 Patient is able (i.e. sufficiently fluent) and willing to complete the health and demographic, quality of life, and health utilities questionnaires in either English or French. The baseline assessment must be completed within required timelines, prior to registration/randomization. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.14 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.

5.1.15 Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 7 days prior to randomization. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy, bilateral tubal ligation or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.1.16 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the NCIC CTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, response assessment and follow-up.

5.1.17 In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 A candidate for potentially curative surgery or radiotherapy.

5.2.2 Patients with brain metastases are ineligible if they meet at least one of the following criteria:

a) diagnosis within 3 months from randomization

b) untreated brain metastases

c) unstable brain metastasis as defined by:
   - cavitation or hemorrhage in the brain lesion
   - symptomatic state
   - daily prednisone or equivalent use greater than 10 mg

Patients do not need CT/MRI scans to rule out brain metastases unless there is a clinical suspicion of CNS metastases.

5.2.3 Patients with serious illness or medical condition which would not permit the patient to be managed according to the protocol including, but not limited to:

- Any evidence of severe or uncontrolled systemic diseases (i.e. known cases of hepatitis B or C or human immunodeficiency virus (HIV).)
- Patients with active or uncontrolled infections

Screening for chronic conditions is not required, although patients known to have such conditions at screening should not be included.

5.2.4 Women who are pregnant or breastfeeding.

5.2.5 Patients with history of allergic or hypersensitivity reactions to any study drug or their excipients or with a history of allergic reactions attributed to compounds with similar chemical composition to any of the study drugs.

5.2.6 Planned concomitant participation in another clinical trial of an experimental agent, vaccine or device. Concomitant participation in observational studies is acceptable.

5.2.7 Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for $\geq$ 5 years. Prior prostate cancer is allowed provided that it is an incidental finding at cystoprostatectomy with a PSA < 0.5 ng/mL at randomization or a prior diagnosis of low risk prostate cancer at any time as defined by $\leq$ T2, a Gleason Score of 6 or less, and PSA < 10 ng/mL.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	History,*including: • histological diagnosis of TCC and documentation of mixed histology • prior therapy, concurrent illness / medications Physical exam,** including : • height, weight, BSA • ECOG performance status	within 14 days prior to randomization
Hematology	• hemoglobin • WBC • neutrophils • platelet count	
Biochemistry	• serum creatinine • bilirubin • ALT	
Radiology***	• CT scan chest, abdomen and pelvis • bone scan • other scans to document disease	within 28 days prior to randomization
Other Investigations	• clinical lesions status ****	
	• pregnancy test♦	within 7 days prior to randomization
	• whole blood♦♦ (*optional*)	after patient consent is obtained
	• formalin fixed, paraffin embedded tissue blocks♦♦+ (*optional*)	after patient consent is obtained
	• Health and Demographic Questionnaire♦♦♦	prior to randomization
Adverse Event++	baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	within 14 days prior to randomization
Quality of Life	• EORTC-C15-PAL (see Appendix VI) • FACT-Taxane (see Appendix VI)	within 7 days prior to randomization
Health Utilities	• EQ-5D Questionnaire	

* Including date of initial diagnosis, TNM stage at diagnosis, and prior administration of all cancer therapy for urothelial cancer, including intravesical, neoadjuvant or adjuvant therapy, surgery, radiation, chemotherapy, biological and experimental agents, bone targeting agents such as bisphosphonates or Rank ligand inhibitors.

** A complete physical exam needs to be performed at screening (including tumour measurements of palpable disease).

*** Obtain chest/abdomen/pelvis CT scans (CT scans preferred, but MRI is acceptable for patients with increased risk of contrast related nephropathy (or other contraindication)). A brain scan is not mandated unless patients have signs or symptoms of CNS disease). Baseline and subsequent imaging (CT or MRI) must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Patients with any type of scan performed as standard of care, prior to consent for this study, within 28 days, of study enrollment that is available at the same facility, where subsequent scans will be performed, will NOT be required to have a repeat scan unless there are new signs or symptoms of disease. CT scans should be performed as per RECIST criteria 1.1.

**** For the purposes of this study evaluation of clinical lesion status is defined as the assessment of superficial lesions such as skin nodules and palpable lymph nodes.

♦ Women of childbearing potential only (urine or serum test acceptable).

♦♦ Optional for consenting patients only.

♦♦♦ In the circumstance that a patient completes the health and demographic questionnaire but is not randomized to the study then the questionnaire must be destroyed by the centre.

+ One tumour block and one adjacent normal tissue block are requested from any of the biopsies or resections of the primary bladder TCC tumour. If no primary cancer blocks are available, one block of metastatic tissue can be sent instead.

++ Adverse events to be evaluated using the NCI CTCAE version 4.0.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All registration/randomizations will be done through the NCIC CTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the BL.12 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the BL.12 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with NCIC CTG.

The following information will be required:

- trial code (NCIC CTG BL.12)
- investigator NCIC CTG user ID
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking consent version date
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- BSA, height and weight
- stratification factors

7.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2, the actual surface area or 2.2 may be used.

7.3 Stratification

Subjects will be stratified by:

- Centre
- ECOG performance status (0, 1 versus 2)
- Liver metastases (yes versus no)
- Lymph node metastases only (yes versus no)
- Hemoglobin (< 100 g/L versus $\geq$ 100 g/L)
- Interval from last platinum based chemotherapy ($\leq$ 6 months versus > 6 months)

7.4 Registration/Randomization

Registration/Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the followup of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration/randomization.

All randomized patients are to be followed until death or until sites are informed by NCIC CTG that further follow-up is no longer required. The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus an annual short followup form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

8.0 TREATMENT PLAN

Although the NCIC Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

8.1 Chemotherapy Treatment Plan

8.1.1 *Drug Administration*

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	Nab-Paclitaxel	260 mg/m^2	IV	Until disease progression or unmanageable toxicity or withdrawal of consent	every 21 days
2	Paclitaxel	175 mg/m^2	IV		

ARM 1:

8.1.2 *Premedication (Arm 1)*

Hypersensitivity reactions are not expected with nab-paclitaxel. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment (e.g. dyspnea requiring bronchodilators, angioedema or generalized urticaria) require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who develop severe hypersensitivity reactions to nab-paclitaxel may be re-challenged following premedication that the institution would typically use for paclitaxel.

8.1.3 *Dose Adjustments (Arm 1)*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

All dosing for chemotherapy will be based on the patient's height and actual body weight (used for calculation of the BSA). Review for dose modifications will be assessed on Day 1 (up to two days before treatment day) of each cycle based on laboratory values or physical signs. If treatment cannot be administered, initiation of the cycle should be delayed.

There will be no re-escalation of dose after reduction for adverse events. Patients may undergo a maximum of 2 dose reductions for adverse events. If a third dose reduction is required, then paclitaxel must be permanently discontinued.

Dose Adjustments for Nab-paclitaxel:

Dose level:	Starting Dose (dose level 0)	1st Reduction (dose level -1)	2nd Reduction (dose level -2)	3rd Reduction (dose level -3)
Nab-Paclitaxel	260 mg/m^2	220 mg/m^2	180 mg/m^2	discontinue

The major toxic effects of Arm 1 which limit dose are hematological (neutropenia, thrombocytopenia), sensory neuropathy, hepatic toxicity, and gastrointestinal toxicity. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

8.1.4 *Hematologic Adverse Events (Arm 1)*

Treatment Day Counts:			
Absolute Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Nab-Paclitaxel Dose Management
≥ 1.0	and	≥ 75	No dose change
< 1.0	and/or	< 75	• Hold until recovery of absolute neutrophils to ≥ 1.5 x 10^9/L and platelets to ≥ 100 x 10^9/L • If counts recover within 7 days, resume nab-paclitaxel at the same dose • If count recovery takes longer than 7 days*, resume nab-paclitaxel at 1 dose level lower
* if not recovered within 3 weeks, discontinue nab-paclitaxel permanently			

8.1.5 *Non-hematologic Adverse Events (Arm 1)*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

Hepatic Toxicity:
Patients who develop abnormal liver function tests, will have the following dose reductions:

Bilirubin		ALT	Nab- Paclitaxel Dose Modification
≤ 1.5 x ULN	and	< 2.5 x ULN	No dose change
≤ 1.5 x ULN	and	≥ 2.5 and 5 x ULN	Reduce to dose level - 1
		> 5 x ULN	Hold drug** and resume when ALT≤ 2.5 x ULN, at dose level -1
> 1.5 x ULN	and	< 2.5 x ULN	Hold drug** until bilirubin <1.5 x ULN, then resume at dose level -1
		> 2.5 and 5 x ULN	Hold drug** until bilirubin <1.5 x ULN and ALT≤ 2.5 x ULN then resume at dose level -1
		> 5 x ULN	Discontinue protocol treatment
** maximum hold for 21 days; if no recovery after 21 days, discontinue nab-paclitaxel			

	Management / Next Dose of Nab-Paclitaxel
Gastrointestinal toxicity:	
• ≥ grade 3 mucositis or diarrhea	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower **
• grade 4: mucositis or diarrhea	Permanently discontinue
Sensory and Motor Neuropathy:	
• ≥ grade 2	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower **
• ≥ grade 3	Permanently discontinue
Hypersensitivity Reactions (grade as Allergic Reaction / Hypersensitivity, CTCAE v 4.0):	
• hypersensitivity reactions are not expected with nab-paclitaxel.	
Other Non-Hematological Adverse Events (not specifically addressed above):	
• grade ≤ 2	Continue nab-paclitaxel and manage symptomatically if possible
• grade 3***	Hold until recovery to ≤ grade 2*. Then resume at 1 dose level lower 1**
• grade 4***	Off nab-paclitaxel therapy♦
* if not recovered within 2 weeks, discontinue nab-paclitaxel permanently. If the toxicity recurs in a subsequent cycle at a grade 3 or higher, the patient should be removed from study treatment and followed for disease progression.	
** may receive a dose reduction or permanently discontinue. This decision will depend upon the type of non-hematologic toxicity seen and which course of action is medically most sound in the judgment of the physician investigator.	
*** this does not include alopecia, anemia, pain, signs/symptoms of androgen deprivation, nausea, cough, headache, insomnia, nail changes, changes in taste and non-symptomatic laboratory values (e.g. sodium, potassium, magnesium)	
♦ the patient should be discontinued from study treatment and followed for disease progression	

8.1.6 *Duration of Therapy (Arm 1)*

Patients are to receive therapy until disease progression, unmanageable toxicity, or withdrawal of consent.

ARM 2:

8.1.7 *Premedication (Arm 2)*

Paclitaxel premedication should be given according to the institutional standard procedures.

8.1.8 *Dose Adjustments (Arm 2)*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

All dosing for chemotherapy will be based on the patient's height and actual body weight (used for calculation of the BSA). Review for dose modifications will be assessed on Day 1 (up to two days before treatment day) of each cycle based on laboratory values or physical signs. If treatment cannot be administered, initiation of the cycle should be delayed.

There will be no re-escalation of dose after reduction for adverse events. Patients may undergo a maximum of 2 dose reductions for adverse events. If a third dose reduction is required, then paclitaxel must be permanently discontinued.

Dose Adjustments for Paclitaxel:

Dose level:	Starting Dose (dose level 0)	1st Reduction (dose level -1)	2nd Reduction (dose level -2)	3rd Reduction (dose level -3)
Paclitaxel	175 mg/m^2	135 mg/m^2	100 mg/m^2	discontinue

The major toxic effects of Arm 2 which limit dose are hematological (neutropenia, thrombocytopenia), hypersensitivity reactions, sensory neuropathy, hepatic toxicity, and gastrointestinal toxicity. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please follow the most conservative dose adjustment recommended.

8.1.9 *Hematologic Adverse Events (Arm 2)*

Treatment Day Counts:			
Absolute Neutrophils (x10^9/L)		Platelets (x10^9/L)	Paclitaxel Dose Management
≥ 1.0	and	≥ 75	No dose change
< 1.0	and/or	< 75	• Hold until recovery of absolute neutrophils to ≥ 1.5 x 10^9/L and platelets to ≥ 100 x 10^9/L • If counts recover within 7 days, resume paclitaxel at the same dose • If count recovery takes longer than 7 days*, resume paclitaxel at 1 dose level lower
* if not recovered within 3 weeks, discontinue paclitaxel permanently			

8.1.10 *Non-hematologic Adverse Events (Arm 2)*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

Hepatic Toxicity:
Patients who develop abnormal liver function tests, will have the following dose reductions:

Bilirubin		ALT	Nab- paclitaxel Dose Modification
≤ 1.5 x ULN	and	< 2.5 x ULN	No dose change
≤ 1.5 x ULN	and	≥ 2.5 and 5 x ULN	Reduce to dose level - 1
		> 5 x ULN	Hold drug** and resume when ALT ≤ 2.5 x ULN, at dose level -1
>1.5 x ULN	and	< 2.5 x ULN	Hold drug** until bilirubin <1.5 x ULN, then resume at dose level -1
		> 2.5 and 5 x ULN	Hold drug** until bilirubin <1.5 x ULN and ALT≤ 2.5 x ULN then resume at dose level -1
		> 5 x ULN	Discontinue protocol treatment
** maximum hold for 21 days; if no recovery after 21 days, discontinue paclitaxel			

	Management / Next Dose of Paclitaxel
Gastrointestinal:	
• ≥ grade 3 mucositis or diarrhea	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower **
• grade 4: mucositis or diarrhea	Permanently discontinue
Sensory and Motor Neuropathy:	
• ≥ grade 2	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower**
• ≥ grade 3	Permanently discontinue
Hypersensitivity Reactions (grade as Allergic Reaction / Hypersensitivity, CTCAE v 3.0):	
• grades 0-1	Slow the rate of infusion of the drug until resolution of symptoms, then resume the planned infusion rate
• grades 2-3	– Stop infusion. Treat as per local protocol or give hydrocortisone or dexamethasone IV, diphenhydramine 50 mg IV, and/or an H2 blocker (e.g. Cimetidine 300m g), at the discretion of the attending physician. – Once recovered, may restart infusion slowly to complete infusion – Next cycle: may re-challenge giving the drug as per protocol
• grade 4 (life threatening anaphylaxis)	Permanently discontinue
Other Non-Hematological Adverse Events (not specifically addressed above):	
• grade ≤ 2	Continue paclitaxel and manage symptomatically if possible
• grade 3***	Hold until recovery to ≤ grade 2*. Then resume at 1 dose level lower 1**
• grade 4	Off paclitaxel therapy♦

* if not recovered within 2 weeks, discontinue paclitaxel permanently. If the toxicity recurs in a subsequent cycle at a grade 3 or higher, the patient should be removed from study treatment and followed for disease progression.

** may receive a dose reduction or permanently discontinue. This decision will depend upon the type of non-hematologic toxicity seen and which course of action is medically most sound in the judgment of the physician investigator.

*** this does not include alopecia, anemia, pain, signs/symptoms of androgen deprivation, nausea, cough, headache, insomnia, nail changes, changes in taste and non-symptomatic laboratory values (e.g. sodium, potassium, magnesium)

♦ the patient should be discontinued from study treatment and followed for disease progression

8.1.11 *Duration of Therapy (Arm 2)*

Patients are to receive therapy until disease progression, unmanageable toxicity, or withdrawal of consent.

8.2 Concomitant Therapy

8.2.1 *Permitted*

Antiemetics:
Dose modification for nausea and vomiting should not be made until patients are on adequate doses of antiemetics. For prevention of acute emesis, a combination of a 5-HT3 receptor antagonist, dexamethasone and aprepitant pre- and post-chemotherapy is recommended for the first 24 hours. For the prevention of delayed emesis, a two-drug combination of dexamethasone and aprepitant is recommended for 2-4 days. For refractory emesis, metoclopramide may be useful. Site guidelines for highly emetogenic chemotherapy should be followed.

Growth Factors and Blood Products:
Filgrastim (G-CSF), pegfilgrastim, erythropoietin and other growth factors may be utilized at the discretion of the Investigator.

Bisphosphonates and Bone Targeted Agents:
Changes in bisphosphonate usage and/or bone protecting agents such as denosumab should not occur until after disease progression is documented (unless the deletion or change is for toxicity associated with usage of these drugs). If the patient is not on a bisphosphonate or denosumab at study entry, they should not be initiated until disease progression is documented so as not to confound disease progression or survival during the study. However, bisphosphonate therapy is allowed to commence after randomization for the treatment of hypercalcemia. All administration of bisphosphonates or denosumab (or any change in usage) during study treatment should be documented, along with the reason for the change.

8.2.2 *Not permitted*

Anti-Cancer Treatment Other Than Protocol Therapy:
Treatment with any other anticancer therapy, including radiation therapy, is not allowed and is considered a protocol violation unless the patient has documented disease progression or has terminated further study treatment. Anticancer therapies include but are not limited to, other chemotherapy, immunotherapy, experimental therapy or radiation therapy.

Concomitant Medications that Inhibit or Induce CYP2C8 or CYP3A4:
The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal drug interaction studies, caution should be exercised when administering nab-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

Herbal Medicine:
Patients should not use St. John's Wort as an herbal medicine during study treatment due to its induction of the cytochrome P450 hepatic enzyme system and possible interference with study treatment.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation During Protocol Treatment

Investigations		Timing
Physical Exam including:	• weight, BSA • ECOG performance status • concurrent medications	day 1 of each cycle*
Hematology**	• hemoglobin • WBC • neutrophils • platelet count	day 1 of each cycle*
Biochemistry**	• serum creatinine • bilirubin • ALT	day 1 of each cycle*
Radiology***	• CT scan chest, abdomen and pelvis • bone scan♦ • other scans to document disease	every 6 weeks♦♦
Other Investigations	• clinical lesions status♦♦♦	every 6 weeks♦♦♦
	• pregnancy test+	at investigator discretion
Adverse Events++	• Patients must be evaluated after each cycle for adverse events	day 1 of each cycle*
Quality of Life	• EORTC-C15-PAL (see Appendix VI) • FACT-Taxane (see Appendix VI)	days 5 -7 of cycle 1 and 2+++, day 1 of cycle 4 and then day 1 of every 4 cycles thereafter
Health Utilities	• EQ-5D Questionnaire	days 5 -7 of cycle 1 and 2+++, day 1 of cycle 4 and then day 1 of every 4 cycles thereafter

* 1 cycle = 21 days, more frequently if clinically indicated.

** Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.

*** To ensure compatibility, the baseline and subsequent radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner).

♦ Bone scan should be repeated only if positive at baseline to confirm CR or PR, and as clinically indicated at other times.

♦♦ Since the primary endpoint for this study is PFS, radiology must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1). Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a radiology scan is done off schedule (e.g. early at 4 weeks), future protocol-required scans should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule scan).

♦♦♦ For the purposes of this study evaluation of clinical lesion status is defined as the assessment of superficial lesions such as skin nodules and palpable lymph nodes. Since the primary endpoint for this study is PFS, clinical lesion status assessment must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1). Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a clinical lesion status assessment is done off schedule (e.g. early at 4 weeks), future protocol-required clinical lesion status assessments should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule assessment).

+ Women of childbearing potential only (urine or serum test acceptable).

++ Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

+++ Patients will be given the questionnaires while in clinic on day 1 of cycle 1 and 2 and asked to complete the questionnaire on day 5 – 7 of cycle 1 and 2 at home. Sites are to contact the patient by telephone on day 5 of both cycles to remind the patient to complete the questionnaire and return it to clinic at their next visit.

9.2 Evaluation After Protocol Treatment

After protocol treatment has been stopped, follow up is required at 6 weeks from the date of off protocol therapy (Post Treatment Follow-up Report) and then at 6 week intervals, until death. A Follow up Report should be used to capture follow-up information prior to progression and a Short Follow-up Report should be used after progression.

Investigations		Timing
Physical Exam including:	• weight, ECOG performance status	at the 6 week follow up visit and at each visit until PD
	• concurrent medications	at 6 week follow up visit only
Hematology	• hemoglobin • WBC • neutrophils • platelet count	at 6 week follow up visit only
Biochemistry	• serum creatinine • bilirubin • ALT	at 6 week follow up visit only
Radiology*	• CT scan chest, abdomen and pelvis • bone scan** • other scans to document disease	every 6 weeks*** until PD
Other Investigations	• clinical lesions status****	every 6 weeks**** until PD
	• pregnancy test♦	at investigator discretion, up until 6 wks post treatment
Adverse Events	Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).	at 6 week follow up visit; at subsequent follow up visits♦♦
Quality of Life	• EORTC-C15-PAL (see Appendix VI) • FACT-Taxane (see Appendix VI)	at every 6 week visit until PD or the initiation of another chemotherapy treatment
Health Utilities	• EQ-5D Questionnaire	at 6 week follow up visit only

* To ensure compatibility, the baseline and subsequent radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner).

** Bone scan should be repeated only if positive at baseline to confirm CR or PR, and as clinically indicated at other times.

*** Since the primary endpoint for this study is PFS, radiology must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1) until progression. Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a radiology scan is done off schedule (e.g. early at 4 weeks), future protocol-required scans should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule scan).

**** For the purposes of this study evaluation of clinical lesion status is defined as the assessment of superficial lesions such as skin nodules and palpable lymph nodes. Since the primary endpoint for this study is PFS, clinical lesion status must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1) until progression. Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a clinical lesion status assessment is done off schedule (e.g. early at 4 weeks), future protocol-required clinical lesion status assessments should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule assessment).

♦ Women of childbearing potential only (urine or serum test acceptable).

♦♦ After the 6 week follow up visit, only Adverse Events deemed related to protocol therapy should be reported.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Progression Free Survival*: Progression free survival is defined as the time interval between the date of randomization and the date of disease progression or death from any cause, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last adequate disease assessment. Disease progression is defined as objective (radiological / clinical) progression (see sections 10.2.5 and 10.2.6 for definitions of radiological progression and section 10.5.1 for definition of clinical lesions).

10.1.2 *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.

10.1.3 *Clinical Benefit Response Rate*: The clinical benefit response rate applies to all patients. It is defined as 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). The response criteria applicable to patients with measurable disease at baseline (Response Evaluation Criteria in Solid Tumours - RECIST) are defined in section 10.2.5. The response criteria applicable to patients without measurable disease at baseline are defined in section10.2.6.

10.1.4 *Evaluable for Adverse Events:* All patients will be evaluable for adverse event evaluation from the time of their first treatment.

10.1.5 *Evaluable for Response:* All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*.

10.1.6 *Evaluable for Quality of Life Assessment*: All patients who have completed the quality of life questionnaire are evaluable for quality of life.

10.1.7 *Evaluable for Health Utilities:* All patients who have completed the baseline health utilities assessment questionnaire and at least one other health utilities assessment questionnaire are evaluable.

10.1.8 *Evaluable for Health and Demographic Assessment*: All patients who have completed the health and demographic questionnaire are evaluable for the health and demographic assessment.

10.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee.

10.2.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

10.2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

10.2.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

10.2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

10.2.5 *Response*.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]*) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

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 on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 4: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	tumour nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	tumour nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.2.6 *Response - Patients With Non-Measurable Disease Only*

Patients with only non-measurable disease, will be assessed for the Clinical Benefit Response Rate endpoint (i.e. will not be considered for the Overall Objective Response Rate endpoint). Prior to inclusion in the rate calculation, each patient will have their BEST OVERALL RESPONSE on study classified as outlined below:

Stable Disease (SD): steady state of disease. No new lesions and not sufficient progression of non-target lesions to qualify for PD.

Progressive Disease (PD): the appearance of new lesions and/or unequivocal progression of non-target lesions.

Non-Measurable Lesions*	New Lesions	Overall Response	Best Overall Response for this category also requires
Complete disappearance	No	SD	documented at least once ≥ 4 wks. from baseline
Non-PD	No	SD	
PD**	No	PD	no prior SD
Any	Yes	PD	

* Note that these lesions should be recorded under the "Non-Target" lesions table on the CRFs

** Unequivocal progression in non-measurable lesions will be accepted as disease progression.

Note:

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic progression". This is a reason for stopping therapy, but is NOT objective PD. Every effort must be made to document the objective progression even after discontinuation of treatment.

10.3 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.4 Stable Disease Duration

Stable disease duration will be measured from the time of start of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.5 Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

10.5.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

10.5.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

10.5.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

10.5.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

10.5.6 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the NCIC CTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the product monograph.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the NCIC CTG Generic Data Management Guidebook for EDC Studies posted on the BL.12 section of the NCIC CTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to NCIC CTG via EDC system.
Within 10 days:	Update Serious Adverse Event Report as much as possible and submit report to NCIC CTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

Gail McDonald, Study Coordinator
NCIC Clinical Trials Group
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the BL.12 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to NCIC CTG as indicated above. Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the NCIC CTG Safety Desk for further instructions (613-533-6430).

11.3 Other Protocol Reportable Events – Pregnancy/Exposure Reporting

In accordance with NCIC CTG's inclusivity in research policy, women of childbearing potential (WOCBP) may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes the potential for unidentified risks to the embryo/fetus. It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

11.3.1 *Pregnancy Prevention*

WOCBP and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in the eligibility criteria 5.1.15. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

11.3.2 *Pregnancy Occurring in WOCBP Exposed to Study Agent*

Any female participant who becomes pregnant during the course of the trial should stop taking study medication immediately.

The investigator should provide counselling and discuss the risks and possible side effects to the embryo/fetus from nab-paclitaxel or paclitaxel. Monitoring should continue until conclusion of the pregnancy. The same should occur for female partners of a male participant, or any female exposed to nab-paclitaxel or paclitaxel when appropriate and compliant with local policy.

11.3.3 *Pregnancy/Exposure Reporting*

The investigator is required to report to the Sponsor any pregnancy where the embryo/fetus could have been exposed to nab-paclitaxel or paclitaxel. This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring up to 30 days after the completion of nab-paclitaxel or paclitaxel must also be reported.

The investigator is required to inform NCIC CTG within 24 hours of learning of the pregnancy using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: “pregnancy, puerperium and perinatal conditions – other, specify” (fetal exposure). Please note that the NCIC CTG patient identification number must correspond to the participant in the main trial. Specifically, in the case of pregnancy in the female partner of a male participant, the male participant’s patient identification number should be used for reporting purposes.

The SAE form must be updated to reflect the outcome of the pregnancy. For example:

- “pregnancy, puerperium and perinatal conditions – other, specify” (normal live birth),
- “pregnancy, puerperium and perinatal conditions – other, specify” (therapeutic abortion), or
- another term under "pregnancy, puerperium and perinatal conditions" as applicable.

Information on the medical history of the parents that may relate to assessing any potential fetal outcomes is requested, as is information on the health of the newborn. The narrative section of the SAE form should be used to communicate all relevant information pertaining to the pregnancy.

In cases where informed consent has not yet been obtained and cannot be obtained within 24 hours, the investigator is expected to report the pregnancy within this timeframe and subsequently amend the SAE form to provide the remaining information once consent has been obtained.

11.4 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

11.5 NCIC CTG Reporting Responsibility to Celgene

Celgene will be notified of nab-paclitaxel reportable serious adverse events within 24 hours of receipt by NCIC CTG.

11.6 Celgene Reporting Responsibilities

Celgene will notify NCIC CTG of all nab-paclitaxel Safety Letters/Safety Updates (SUs) or Serious Adverse Events (SAEs) that they reported to regulatory authorities from other trials.

11.7 Reporting Safety Reports to Investigators

NCIC CTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the NCIC CTG trial BL.12 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the NCIC CTG trial BL.12 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by NCIC CTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Tumour progression or disease recurrence as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment

Patients are to receive therapy until disease progression, unmanageable toxicity, or withdrawal of consent

12.3 Therapy After Protocol Treatment is Stopped

After protocol treatment is stopped, therapy is at the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

Follow-up will continue after treatment completion according to the plan described in the protocol (see section 9.2 and Appendices I and IV).

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

There will be no central radiology review for this study.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Tissue Collection

Pharmacogenomics (Optional)
A whole blood sample will be collected at baseline on all consenting patients for pharmacogenomic studies for the purposes described in section 2.4.2. Evaluation of genetic polymorphisms will be very important in furthering our understanding of response and toxicity to the therapeutic agents used in this protocol.

It is requested that one 10-cc EDTA purple top tube (whole blood) is obtained for pharmacogenomic testing at baseline. This whole-blood tube is only collected once per patient. Upon collection the sample should be aliquoted into five 2cc labelled cryotubes, and stored at -80°C or greater, until shipment to the NCIC CTG Tumour Tissue Data Repository (TTDR). A maximum of 1.5 mL of whole blood should be aliquoted per cyrotube. Freezer compatible labels should be used for labeling cryotubes. Labels should be affixed to cryotubes prior to collection of specimens and should be filled out using a permanent marker appropriate for storage in the freezer and/or for use on dry ice. Please note that local supplies should be used. All submitted specimens from consenting patients must be labelled with the treatment protocol number, NCIC CTG patient number, patient's initials and date of collection. A BL.12 label template guide is available on the BL.12 trial specific webpage to aid in the producing a cryotube label for this study. Whole blood samples can be batched and shipped every 6 months to the TTDR.

Formalin Fixed Paraffin Embedded Tissue Acquisition for Correlative Sciences (Optional)
In those cases where tumour samples from patients treated on study are available and informed consent has been obtained, tumour samples will be submitted and stored at NCIC CTG Tumour Tissue Data Repository. One tumour block and one adjacent normal tissue block are requested from any of the biopsies or resections of the primary bladder TCC tumour. If no primary cancer blocks are available, one block of metastatic tissue can be sent instead. For cases in which local centre regulations prohibit submission of blocks of tumour tissue, please contact the Study Coordinator as cores (two 2 mm cores of tumour from the block(s)) may be an acceptable alternative. If tumour blocks are not available, 30 unstained paraffin slides (4 to 5 microns) that are suitable for IHC and FISH are acceptable.

Collection of Tumour Tissue for Tumour Banking (Optional)
The collection of a representative block of the diagnostic tumour tissue (if available) is an important component of this study. This is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks will be carefully banked as part of the NCIC CTG tissue/tumour bank at Queen's University in Kingston, Ontario. Tumour blocks will be the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of urothelial cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to pathology departments for a representative tumour block.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

Please ship all tumour blocks and frozen blood specimens to:

Shakeel Virk
Pathology Coordinator
Queens University
NCIC Clinical Trials Group*
Richardson Labs Building, 4-th Floor
88 Stuart Street, Kingston ON K7L 3N6
Tel: (613) 533-2906
Fax: (613) 548-2486
E-mail: virk@cliff.path.queensu.ca

* Hours of operation for the NCIC CTG Tissue Bank are Monday to Friday, 8:00 am to 4:00 pm EST. NCIC CTG is closed during weekends and observed holiday. Please plan to ship all frozen specimens on a Monday, Tuesday or Wednesday of the week to avoid any weekend deliveries.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This will be a randomized, open-labelled, multicentre trial where in patients with advanced urothelial cancer failing one line of platinum based therapy will be randomized to either nab-paclitaxel or paclitaxel with a 1:1 ratio. Patients randomization procedure will be 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).

The primary objective is to compare PFS between Arm 1 and Arm 2, among all randomized patients. 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.

14.2 Endpoints and Analyses

All randomized patients will be evaluable for the primary endpoint of PFS and the secondary endpoint of OS. Patients will be evaluable for objective tumour response if they have at least one disease assessment after baseline. In addition, patients who develop PD prior to this time will also be considered evaluable for response. Time to response and duration of response will be calculated for all patients achieving a PR or CR. All patients who receive at least one dose of nab-paclitaxel or paclitaxel will be included in the safety summaries.

PFS is defined as the time from randomization to the first observation of 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 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. In the primary analysis, the comparison between the two treatment arms will be tested using the log-rank test stratified by 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). All randomized patients will also be included in the survival analysis. A Kaplan-Meier *[Kaplan 1958]* curve for proportions of survival over time during the trial in each treatment arm will be displayed.

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. Survival distribution of time to event variables including duration of response and stable or responding disease will be estimated by Kaplan-Meier (K-M) curves for each treatment arm. The 95% confidence intervals for the median survival will be computed using the method of Brookmeyer and Crowley.

Time to response is defined as the time from the first dose of study drug until the first objective status assessment of CR/PR among those who achieved a CR or PR. Time to complete response is defined as the time from the first dose of study drug until the first objective status assessment of CR. The duration of response is defined as the time from 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. Similar analyses will be performed for time to response and stable or responding disease including patients who have achieved CR, PR or stable disease.

Quality of Life Analyses

Quality of life will be assessed using the EORTC-C15-PAL questionnaire plus additional study specific questions.

Changes in quality of life scores while on treatment (compared to baseline scores) will be examined using descriptive analyses and inferential statistics. The primary test to compare treatment arms will be a Wei-lachin test for stochastic ordering, including all time points where QoL was measured. In addition, baseline scores between arms will be compared using a Wilcoxon rank sum test, and a pattern mixture model identifying drop-out patients as a special category will be performed to evaluate the effect of missing data.

Additional analyses will be conducted using NCIC CTG standard analysis programs. Between group comparison will include the analysis of mean scores over time, as evaluated at 5-7 days after cycle 1 and 2 and at each clinic visit: 3, 6, and 12 weeks, then every 12 weeks (until initiation of another chemotherapy or disease progression); lower mean scores and a smaller area-under-the-curve will be used as the main analyses. A comparison of the proportion of patients experiencing a clinically important adverse change in neuropathy scores will also be evaluated. In addition, a comparison of the proportion of patients changed from baseline (either for better or for worse) will be calculated using the NCIC CTG standard analysis program. A minimal change of 10 points (on a normalized scale of 0-100 for all relevant domains and item scores) will be used to calculate the respective proportions.

Economic Analyses

The purpose of the economic evaluation is to determine the incremental cost-effectiveness and cost-utility of nab-paclitaxel from a government payer perspective, over a lifetime time horizon by prospectively collecting economic and resource utilization information during the clinical trial.

The objectives are:

a) determine an incremental cost effectiveness ratio reported as a cost per life-year (LY) gained of nab-paclitaxel vs. paclitaxel. A cost-effectiveness analysis will be conducted. The mean overall cost per patient for each of the two study treatment arms will be calculated to determine the additional cost per life-year gained.

b) determine an incremental cost utility ratio in cost per quality-adjusted life-year (QALY) gained of nab-paclitaxel vs. paclitaxel. A cost-utility analysis will be conducted. Preference weights for comparator arms will be determined. Health states will be determined from the study database, which will enable calculation of the quality-adjust survival of patients in the two treatment arms by multiplying the utility value by the amount of time spent in that utility state. The mean overall cost per patient for each of the two study treatment arms will be calculated.

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, chemotherapy and survival, will be varied +/- 20%, to examine the impact on the base-case incremental cost effectiveness ratios (ICERs). Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted.

Correlative Study and Pharmacogenomics Analyses

For all consenting patients, archival diagnostic tumour tissue and baseline whole blood will be collected and banked.

The following analyses will be performed for each treatment regimen. Descriptive statistics will be used to summarize biomarkers for responders versus to assess relationship between response and biomarkers, a logistic regression analysis will be performed with effects for biomarker and treatment regimen in the model. To assess the relationship of overall survival (and PFS) with biomarkers, a Cox regression analysis will be used with effects for biomarker and treatment regimen in the model. In addition, for SPARC and other biomarkers with binary measures, survival will be summarized by median survival time for each biomarker category along with the hazard ratio. For each treatment regimen, the Kaplan-Meier curve for survival will be presented graphically for each biomarker category and differences in the curves will be tested using the log-rank test.

Health and Demographic Questionnaire Analyses

Much of the analyses of this questionnaire involve the inclusion of elements of the HDQ as confounders or potential interactors with QoL, health economics, correlative, co-morbidity and baseline patient characteristics, and other HDQ elements for the primary and secondary outcome measures. As such, these analyses are described in the appropriate correlative, QoL, and health economic sections. The HDQ data will also be used in a descriptive manner (i.e. comparing the BL.12 trial population with demographic data derived from the larger non-trial population of patients). When quantitative analyses are needed to understand how the HDQ variable affects other potential confounders or primary and secondary outcomes, regression methods will be utilized.

14.3 Sample Size and Duration of Study

Assuming a median survival of 4 months with paclitaxel, the study is designed to detect a one third reduction in the hazard of 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 81% power, 155 events are required. This will 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 will be approximately 199 patients which will allow for lost to follow-up or withdrawal of consent.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings. There will be safety monitoring by the DSMC after 50 patients have been accrued as well as every 6 months. Particular attention will be paid to fatal adverse events, deaths within 30 days of study drug, bleeding, thrombosis and differential toxicity related to histological subtype.

Descriptive summary tables will be presented on safety parameters by treatment arm. Toxicity rates will be compared between treatment arms using the Fisher’s Exact Test, as needed.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the NCIC Clinical Trials Group, Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP), NHMRC Clinical Trials Centre, and Celgene, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with the health economic outcomes, the first author will generally be the Health Economics Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the NCIC Clinical Trials Group and conducted in collaboration with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group, and the NHMRC Clinical Trials Centre. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

NCIC CTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the NCIC CTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Celgene, ANZUP, the NHMRC Clinical Trials Centre Clinical Lead, the NCIC CTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

16.2 Inclusivity in Research

NCIC CTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of NCIC CTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a NCIC CTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is NCIC CTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into NCIC CTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. NCIC CTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an NCIC CTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, NCIC CTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. NCIC CTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

NCIC CTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. NCIC CTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

NCIC CTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the pregnant female is not a participant in the main trial, consent should be obtained via use of the *exposure/*pregnancy follow-up consent form.

In the case of information collected about a newborn, consent should be provided by the legal guardian. In cases where the legal guardian is the participant in the main trial, consent is obtained via the main consent. If the legal guardian is not the trial participant, consent should be obtained via the exposure/pregnancy follow-up consent.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the NCIC CTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the NCIC CTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the NCIC CTG), it is the responsibility of the qualified investigator to notify the NCIC CTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the NCIC CTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by NCIC CTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

NCIC CTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

NCIC CTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Completed Quality of Life and EQ-5D questionnaires should be entered directly into the EDC system by the Clinical Research Associate. The completed Health and Demographic Questionnaire must be scanned and uploaded through the EDC system.

For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the BL.12 area of the NCIC CTG web-site (www.ctg.queensu.ca).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study *(prior to random-ization)*	During Protocol Treatment			After Completion of Protocol Therapy	
		Day 1 of cycle	Days 5 -7 of cycle 1 and 2♥, day 1 of cycle 4 and then day 1 of every 4 cycles thereafter	Every 6 weeks	6 weeks after end of protocol therapy	Every 6 weeks after end of protocol therapy until Progressive Disease
History and Physical Exam						
Medical History*	X					
Physical Examination	X	X			X	X
Concomitant Medications	X	X			X	
Height	X					
Weight	X	X			X	X
BSA	X	X				
ECOG PS	X	X			X	X
Hematology**						
Hemoglobin, WBC, neutrophils, platelet count	X	X			X	
Biochemistry**						
Serum creatinine, bilirubin, ALT	X	X			X	
Radiology***						
CT scan chest, abdomen and pelvis	X			X[1]	X[1]	X[1]
Bone scan	X					
Other scans to document disease	X					
Other Investigations						
Clinical Lesions Status	X			X[2]	X[2]	X[2]
Pregnancy test (*if applicable*)****	X	X[3]			X[3]	
Whole blood *(optional)* ♦	X					
formalin fixed, paraffin embedded tissue blocks *(optional)* ♦+	X					
Health and Demographic Questionnaire♦♦	X					
Adverse Events♦♦♦						
Adverse Event assessment	X	X			X	X[4]
Quality of Life						
EORTC-C15-PAL, FACT-Taxane	X		X♥		X[5]	X[5]
Health Utilities						
EQ-5D Questionnaire	X		X♥		X	

footnotes on next page …

*	Medical History includes histological diagnosis of TCC and documentation of mixed histology, date of initial diagnosis, TNM stage, concurrent illness, prior administration of all cancer therapy for urothelial cancer, including intravesical, neoadjuvant or adjuvant therapy, surgery, radiation, chemotherapy, biological and experimental agents, bone targeting agents such as bisphosphonates or Rank ligand inhibitors.
**	Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
***	Obtain chest/abdomen/pelvis CT scans (CT scans preferred, but MRI is acceptable for patients with increased risk of contrast related nephropathy (or other contraindication)). A brain scan is not mandated unless patients have signs or symptoms of CNS disease). Baseline and subsequent imaging (CT or MRI) must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Patients with any type of scan performed as standard of care, prior to consent for this study, within 28 days, of study enrollment that is available at the same facility, where subsequent scans will be performed, will NOT be required to have a repeat scan unless there are new signs or symptoms of disease. CT scans should be performed as per RECIST criteria 1.1
****	Women of childbearing potential only (urine or serum test acceptable).
♦	Optional for consenting patients
♦♦	In the circumstance that a patient completes the health and demographic questionnaire but is not randomized to the study then the questionnaire must be destroyed by the centre.
♦♦♦	Adverse events to be evaluated using the NCI CTCAE version 4.0.
+	One tumour block and one adjacent normal tissue block are requested from any of the biopsies or resections of the primary bladder TCC tumour. If no primary cancer blocks are available, one block of metastatic tissue can be sent instead.
♥	Patients will be given the questionnaires while in clinic on day 1 of cycle 1 and 2 and asked to complete the questionnaire on day 5 – 7 of cycles 1 and 2 at home. Sites are to contact the patient by telephone on day 5 of both cycles to remind the patient to complete the questionnaire and return it to clinic at their next visit.
1.	Since the primary endpoint for this study is PFS, radiology must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1). Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a radiology scan is done off schedule (e.g. early at 4 weeks), future protocol-required scans should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule scan).
2.	For the purposes of this study evaluation of clinical lesion status is defined as the assessment of superficial lesions such as skin nodules and palpable lymph nodes. Since the primary endpoint for this study is PFS, clinical lesion status assessment must be consistently performed every six weeks counting from the first day of protocol treatment (i.e. day 1, cycle 1). Sites should adhere to this 6 week calendar based schedule regardless of any delays in treatment cycles. If a clinical lesion status assessment is done off schedule (e.g. early at 4 weeks), future protocol-required clinical lesion status assessments should still be performed based on the original schedule, i.e. every six weeks counting from the first day of protocol treatment (not 6 weeks from the date of the off schedule assessment).
3.	At investigator discretion.
4.	After the 6 week follow up visit, only Adverse Events deemed related to protocol therapy should be reported.
5.	At every 6 week visit until PD or the initiation of another chemotherapy treatment.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Note: It is expected that centres will use their commercial supply of paclitaxel for this trial.

General

Nab-paclitaxel will be supplied by Celgene.

Distribution

Please refer to the BL.12 trial specific website for instructions on drug ordering and distribution.

Drug Accountability

It is the responsibility of each site to maintain drug accountability logs for nab-paclitaxel.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Completed Quality of Life and EQ-5D questionnaires should be entered directly into the EDC system by the Clinical Research Associate. The completed Health and Demographic Questionnaire must be scanned and uploaded through the EDC system. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "NCIC CTG EDC Generic Data Management Guidebook" posted on the BL.12 area of the NCIC CTG web-site (www.ctg.queensu.ca).

The electronic CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required	To be completed electronically	Supporting Documentation Required♦
Eligibility Checklist		At the time of randomization	Copies of signed consent form and tissue banking consent* (if applicable); relevant operative pathology and radiology reports
Baseline Report		Within 2 weeks of randomization	
Correlative Studies Report (Tumour and Blood)	Continuous running-log folder	If the patient has consented to optional tissue banking: Information pertaining to **tissue collection** must be completed within 2 weeks of randomization. **Tissue to be submitted immediately upon request.**	Consent form* Diagnostic pathology report (for tumour tissue only)
		If the patient has consented to optional blood banking: Information pertaining to **whole blood collection** must be completed within 2 weeks in which the sample was collected.	
Concomitant Medication Report	Continuous running-log folder		
Treatment Report	Every 3 weeks (21 days) after each cycle	Within 2 weeks of the end of each cycle	Relevant radiology reports
End of Treatment Report	When the patient goes off protocol treatment.	Within 2 weeks of the end of treatment	
Post Treatment Follow-up Report	To be completed once on all patients, 6 weeks after going off protocol treatment.	Due within 2 weeks after contact with patient.	Relevant radiology reports
Follow-up Report	Every 6 weeks until PD (following 6 week Post Treatment Report)	Within 2 weeks of follow-up visit	Relevant radiology reports
Relapse/Progression Report	Upon disease progression	Within 4 weeks of confirmation	Relevant radiology, operative and pathology reports
Short Follow-up Report	Every 6 weeks after PD	Within 2 weeks of follow-up visit	
Death Report	When patient dies**	Within 2 weeks of patient's death	Autopsy /post-mortem report, if done
SAE Report***	At the time of the event	See section 11.0	

* For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.
** It is the investigators responsibility to investigate and report the date and cause of death of any patient entered into this trial.
*** See section 11.0 Serious Adverse Event Reporting for details.
♦ Supporting Documentation should be uploaded into the EDC system/mailed immediately after the eCRF has been submitted electronically.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

   A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

      Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:
      If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QoL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **BL.12**

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

During chemotherapy:

☐ Days 5 - 7 cycle 1 ☐ Days 5 - 7 cycle 2 ☐ Day 1 cycle 4 ☐ Day 1 cycle 8 ☐ Day 1 cycle 12

☐ Day 1 cycle 16 ☐ Day 1 cycle 20 ☐ Day 1 cycle 24 ☐ Day 1 cycle 28 ☐ Day 1 cycle _____

Off Treatment:

☐ week 6

then ☐ wk 12 ☐ wk 18 ☐ wk 24 ☐ wk 30 ☐ wk 36 ☐ wk 42 ☐ wk 48 ☐ wk 54 ☐ wk _____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ___ ___ ___

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (C15-PAL)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in a bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not At All	A Little	Quite a Bit	Very Much
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4
10. Have you been constipated?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ___ ___ ___

During the past week:	Not At All	A Little	Quite a Bit	Very Much
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you.

15. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

FACT-Taxane (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Taxane (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Taxane (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
Tax2	My hands are swollen	0	1	2	3	4
Tax3	My legs or feet are swollen	0	1	2	3	4
Tax4	I have pain in my fingertips	0	1	2	3	4
Tax5	I am bothered by the way my hands or nails look	0	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank You.

APPENDIX VII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX VIII - HEALTH AND DEMOGRAPHIC QUESTIONNAIRE

Instructions for Administration of the Health and Demographic Questionnaire

The instructions below are intended as a guide for the administration of the health and demographic questionnaire.

1. Preamble

   Epidemiologic data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a series of questions which should be completed from the patient's perspective.

   The scheduled time to obtain the questionnaire is:

   - prior to randomization

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If the questionnaire has not been completed, please document the reason(s) on the appropriate case report form.

2. Assessment

   It should be explained to the patient that the purpose of the questionnaire is to collect information such as race and ethnicity, family history, smoking and alcohol exposure, vitamin and medication use as well as demographic data to analyze its relation with the results of the tested treatment.

   This questionnaire should be given to all patients.

   The Health and Demographic Questionnaire should be given to the patient to be completed at his/her home or at the clinic.

   The Clinical Research Associate (CRA) should collect the questionnaire at the next patient clinic visit.

3. What If…

   The patient leaves the clinic and someone forgets to give the questionnaire to the patient:

   - Contact the patient by phone informing him or her that the questionnaire will be mailed.
   - Mail a blank questionnaire to the patient with instruction to be completed with instructions to return the completed questionnaire at the next clinic visit.

4. Inability to Complete the Health and Demographic Questionnaire

   Assistance may be used to complete the questionnaire.

Health and Demographic Questionnaire – ENGLISH

NCIC CTG Trial: **BL.12**

This page to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

THIS QUESTIONNAIRE SHOULD BE TAKEN BACK TO PATIENT'S HOME TO BE COMPLETED, NOT AT THE CLINIC.

Scheduled time to obtain this Health and Demographic Questionnaire:
After patient consent obtained

Date questionnaire completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	RA: _____	Data Ent'd:	Verif:
_____ - _____ - ___	_____ - _____ - ___	_____ - _____ - ___	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

NCIC CTG BL.12 - Health and Demographic Questionnaire

INSTRUCTIONS

- Answer by marking the correct box or filling in the spaces provided.
  Example: ☐ Yes
  ☐ No
- You may skip any question that you do not want to answer
- Some questions have a follow-up question.
  Example: 11. Have you ever tried to quit smoking?
  ☐ No (*go to question 12*)
  ☐ Yes a) How many times?
  __ __ # times

HELPFUL INFORMATION: Some information is used to help describe the patients in our study as a whole. No individual's information will be analyzed alone. If there is a question or there are specific questions that you prefer not to answer, please leave the question(s) blank.

YOUR BACKGROUND

1. **In what country were you born?** _____
   Name of country

2. **In what country were your parents born?** _____ **(*Mother's country of birth*)**
   _____ **(*Father's country of birth*)**

3. **What are your family origins? Check all that apply.**

A. ☐	AFRICAN OR AFRICAN-CARIBBEAN (BLACK)	*Including Africa (excluding North Africa), Caribbean Islands, any other African or African-Caribbean family origins*
B. ☐	SOUTH ASIAN (ASIAN)	*Including India or African-Indian Pakistan Bangladesh*
C. ☐	SOUTH EAST ASIAN (ASIAN)	*Including China including Hong Kong, Taiwan, Singapore, Thailand, Indonesia, Burma, Malaysia, Vietnam, Philippines, Cambodia , Native Hawaiian or other Pacific Islander*
D. ☐	NORTHERN EUROPEAN (WHITE)	*Including Austria, Belgium, Ireland, France, Germany, Netherlands, Scandinavia, Switzerland etc.*
E. ☐	SOUTHERN & OTHER EUROPEAN (WHITE)	*Including Sardinia, Greece, Turkey, Cyprus, Italy, Portugal, Spain, Any other Mediterranean country, Albania, Czech Republic, Poland, Romania, Russia etc.*
F. ☐	OTHER WHITE	*Including United Kingdom, Australia, North America, South Africa*
G. ☐	OTHER NON-EUROPEAN (OTHER)	*Including North Africa, South America, Latino, Hispanic, Middle East (Saudi Arabia, Iran etc.)*

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4. **How much did you weigh at the following ages up until your present decade of life (if you don't know your exact weight, please make your best guess)?**

Age	Weight		
25	_____ kg	or	_____ lbs
35	_____ kg	or	_____ lbs
45	_____ kg	or	_____ lbs
55	_____ kg	or	_____ lbs
65	_____ kg	or	_____ lbs

5. **How much did you weigh 1 year before your diagnosis?** _____ kg

6. **How tall were you (without shoes) at about age 25?** _____ **cm**

7. **How tall are you (without shoes) now?** _____ **cm**

8. **Did you ever or do you drink coffee on a regular basis (1-2 cups per day)?**
   - ☐ Yes
   - ☐ No

9. **If you still drink coffee, how many cups per day on average, do you drink?**
   - ☐ **None**
   - ☐ **Less than 1**
   - ☐ **1-2**
   - ☐ **3-4**
   - ☐ **5 or more**

10. **Have you ever been treated for a *Schistosoma haematobium* infection?**
    - ☐ Yes
    - ☐ No

YOUR OCCUPATION HISTORY

11. **What is (or was) your primary occupation (job) for most of your life and what tasks did you perform?**

Primary Occupation/Job _____

Tasks _____

How long did you work at this occupation? _____ years

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12. If you worked in any of the following industries for more than 6 months during your lifetime, please provide some detailed information about your job environment in the table below:

Industry	Yes	No	Years at this job	Brief Description	Are you presently working at this job? Yes	No
Aluminum production or carbon electrode/ anode -manufacturing	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Coke Production (Coke Oven)	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Dye manufacturing or application (including hairdresser or barber)	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Printing processes (paper dyeing, flexographic printing)	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Pesticide/herbicide manufacturing or application	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Painting	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Rubber industry	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Steel production	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐
Textile industry	☐	☐		Job title:_____ Tasks: _____ _____	☐	☐

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YOUR FAMILY HISTORY

13. Are you adopted? ☐ Yes ☐ No

14. Can you answer questions about your blood (natural) relatives? ☐ Yes ☐ No (*go to question 16*)

15. Please answer the following questions about your natural parents, brothers or sisters, and children. Fill in the table. Do not include aunts, uncles, grandparents or grandchildren, adopted, step or half relatives.

Relationship (*e.g. mother, father, sister, brother, son, daughter*)	**Are they still Alive?**		**How old are they now** (*or how old were they when they died*)?	**Did they ever have cancer?**		**What type(s) of cancers, and their (approximate) age(s) of diagnosis? If you don't know which type, write "Don't know"** *Examples include: Breast, Ovarian, Uterus, Lung, Colon or Rectal, Bladder, Prostate, or Pancreas, Melanoma, Leukemia or Lymphoma, Sarcoma*	
	Yes	**No**		**Yes**	**No**		
Example: Brother #1	☐	☐	49 yrs	☐	☐	colon cancer, 46 yrs	Lymphoma, 30's
Mother	☐	☐	____ yrs	☐	☐		
Father	☐	☐	____ yrs	☐	☐		
Daughter # ____	☐	☐	____ yrs	☐	☐		
Daughter # ____	☐	☐	____ yrs	☐	☐		
Daughter # ____	☐	☐	____ yrs	☐	☐		
Son # ____	☐	☐	____ yrs	☐	☐		
Son # ____	☐	☐	____ yrs	☐	☐		
Son # ____	☐	☐	____ yrs	☐	☐		
Brother # ___	☐	☐	____ yrs	☐	☐		
Brother # ___	☐	☐	____ yrs	☐	☐		
Brother # ___	☐	☐	____ yrs	☐	☐		
Sister # ____	☐	☐	____ yrs	☐	☐		
Sister # ____	☐	☐	____ yrs	☐	☐		
Sister # ____	☐	☐	____ yrs	☐	☐		

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SMOKE EXPOSURE

16. Have you ever used the following tobacco products at least once per day for three months or more? Cigarettes/ Pipes/ Cigars/ Chewing tobacco/ Snuff? *(Go to question 17 if all the answers are "no").*

	Cigarettes at least 1 cig/day for 3 months or more	**Pipes** at least 1 pipe/day for 3 months or more	**Cigars** at least 1 cigar/day for 3 months or more	**Chewing tobacco** at least 1 chewed tobacco/day for 3 months or more	**Snuff** at least 1 snuff of tobacco/day for 3 months or more
Have you ever used the following tobacco products?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
How old were you when you started?	_____ years	_____ years	_____ years	_____ years	_____ years
How many did you use?	_____ No. per ☐ day ☐ week ☐ month	_____ No. per ☐ day ☐ week ☐ month	_____ No. per ☐ day ☐ week ☐ month	_____ No. per ☐ day ☐ week ☐ month	_____ No. per ☐ day ☐ week ☐ month
Have you quit? How old were you when you quit?	☐ No ☐ Yes _____ years	☐ No ☐ Yes _____ years	☐ No ☐ Yes _____ years	☐ No ☐ Yes _____ years	☐ No ☐ Yes _____ years

17. We are interested in your exposure to smoke from other people's cigarettes and tobacco products. Please complete the table below.

Were you exposed to smoke from <u>other</u> people's cigarettes or tobacco products during:	**Yes**	**No**	**For how many hours per day? (Best guess)**	**For how many years? (Best guess)**
Childhood at home	☐	☐	__ __ hours ☐ Don't Know	__ __ years ☐ Don't Know
Adulthood at home	☐	☐	__ __ hours ☐ Don't Know	__ __ years ☐ Don't Know
Adulthood at work	☐	☐	__ __ hours ☐ Don't Know	__ __ years ☐ Don't Know

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PHYSICAL ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in **the last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

18. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ days per week ☐ No vigorous physical activities (*Skip to question 20*)

19. How much time did you usually spend doing vigorous physical activities on one of those days?

_____ hours per day _____ minutes per day ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

20. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week ☐ No moderate physical activities (*Skip to question 22*)

21. How much time did you usually spend doing moderate physical activities on one of those days?

_____ hours per day _____ minutes per day ☐ Don't know/Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

22. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

_____ days per week ☐ No walking (*Skip to question 24*)

23. How much time did you usually spend walking on one of those days?

_____ hours per day _____ minutes per day ☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

24. During the last 7 days, how much time did you spend sitting on a week day?

_____ hours per day _____ minutes per day ☐ Don't know/Not sure

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LIFETIME ALCOHOL USE:

25. During your lifetime, has there ever been a time when you have had at least one alcoholic drink per month for a period of at least 6 months?

☐ Yes (*go to question 26*)
☐ No (*go to question 29, page 8 if you are a woman, and page 9, question 42 if a man*)
☐ Don't Know (*go to question 29, page 8 if you are a woman, and page 9, question 42 if a man*)

26. How old were you when you first started drinking at least 1 glass of alcohol per month for a period of at least 6 months?

__ __ age started drinking alcohol (in years)

27. During the year before you were diagnosed with cancer, did you drink at least 1 glass of alcohol per month period of at least 6 months?

☐ Yes (*go to question 28*)
☐ No, not at all

a) At what age did you stop drinking alcohol? __ __ Age stopped drinking alcohol (in years)

28. Please fill in table. Fill in the period of time using your age, and the average amount you drank for that period. You may use multiple age ranges if your drinking habits have changed over the years. If you are still drinking fill in your current age as the "ending age". One drink means one can/bottle/mug of beer, one 6 ounce glass of wine, or one ounce of hard liquor.

Type of alcohol	Time period Starting age (years)		Time period Ending age (years)	Average weekly consumption of drinks					
				0	1-2	3-5	6-11	12-23	24+
Beer	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
Wine	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
Hard Liquor (e.g. gin, vodka)	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐
	Age __ __ years	To	Age __ __ years	☐	☐	☐	☐	☐	☐

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WOMEN'S HISTORY

Fill in only if you are a woman. If you are a man, proceed to question 42.

29. How old were you when you had your first menstrual period? __ __ Age in years.

- ☐ Never had a period
- ☐ Don't know

30. Have you ever given birth to a child? (*Do not include miscarriages in the first 5 months of pregnancy)*

- ☐ Yes
- ☐ No (*go to question 33)*

31. How old were you when your first child was born? __ __ Age in years.

32. How many times have you given birth? __ __ times in your lifetime

33. Have you had periods in the last year? Mark only one.

- ☐ Yes, but not regularly (*go to question 36*)
- ☐ Yes, because I take hormones (*go to question 36*)
- ☐ Yes, I have had regular periods in the past year (*go to question 36*)
- ☐ No

34. How old were you when your periods permanently stopped? __ __ Age periods stopped (*best guess*)

35. Why did your periods stop?

- ☐ Natural menopause (Change in life)
- ☐ Surgery (such as having your ovaries or uterus removed)
- ☐ Other _____

36. Have you ever used pills, shots, patches or hormone implants for birth control or to regulate periods?

- ☐ Yes
- ☐ No (*go to question 38*)
- ☐ Don't Know (*go to question 38*)

37. How many years (total) did you use pills, shots, patches or hormone implants for birth control or to regulate periods?

__ __ years (best guess)

38. Have you ever used estrogen (hormone) replacement therapy (HRT) to help with menopausal symptoms? Only include pills, shots, patches or hormone implants that require a doctor's prescription. Do not include birth control pills.

- ☐ Yes
- ☐ No (*go to question 42*)
- ☐ Don't Know *(go to question 42*)

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39. How old were you when you first used HRT? _____ age you used HRT (hormones)

40. How many years (total) have you used (or did you use) HRT? _____ years that you used hormones

41. Do you take HRT now?

☐ Yes
☐ No

MEDICATION USE

42. Since you were 18 years old, did you take any of the following medications? Fill in the table. Mark all that apply.

Did you ever take these drugs at least once a week for at least one year?		If Yes, for how long (approximately)?	For how many days every week on average (approximately)?
Acetylsalicylic acid Such as aspirin, Anacin®, Bufferin®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Acetaminophen Such as Tylenol®, Panadol®, Tempra®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Ibuprofen Such as Advil®, Motrin®, Rufen®,Medipren®, Nuprin®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Naproxen Such as Aleve®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Other Anti-Inflammatory Drugs Such as Indocin®, Lodine®, Voltaren®, Relafen®, Clinoril®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Cox-2 Inhibitors Such as Celebrex®, Vioxx®, Bextra®	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)
Cholesterol Statin Medications Such as Lipitor®, ®Zocor, ®Mevacor, ®Pravachol, or ®Crestor	☐ Yes, at least once a week for at least one year ☐ No, not that often	__ __ __ years	☐ <1 days per week ☐ 1-3 days per week ☐ 4-6 days per week ☐ 7 days (every day)

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43. What is the highest level or year of school you have completed? Mark only one.

- ☐ None (0 year)
- ☐ Elementary/Junior High School (≤8 years)
- ☐ High school (≤12 years)
- ☐ College (≤16 years)
- ☐ Graduate/Professional school (>16 years)
- ☐ Don't know
- ☐ Refused

44. What is your marital status?

- ☐ Married
- ☐ Living as married
- ☐ Widowed
- ☐ Separated
- ☐ Divorced (or annulment)
- ☐ Single, never married or never lived as married
- ☐ Don't Know

45. Who filled in this questionnaire?

- ☐ Patient
- ☐ Patient's family member (specify relationship, e.g. wife, etc.) _____
- ☐ Study personnel (specify) _____
- ☐ Other (specify)_____

Please review the questionnaire once more to determine whether any questions you left blank were intentionally skipped.

Thank you for completing this questionnaire!

APPENDIX IX - HEALTH UTILITIES ASSESSMENT

Introduction

Note: Patients from these centres should complete the quality of life assessment before the health utilities assessment.

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, progression free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient’s individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side-effects, *et cetera*.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that she prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule (see Sections 6, 9.1, and 9.2).

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if health economics data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if she is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if she is willing to complete a questionnaire over the phone. If the patient agrees, read out questions 1-5 and range of possibilities, and record the answers. The visual analogue scale should not be completed in this case. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Health Utilities Component

The only time that we will not require a patient to complete the health utilities questionnaires is if she is not literate in either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Health Utilities Questionnaire

If a patient speaks and reads English or French, but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

8. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D Questionnaire in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

EQ-5D Questionnaire – ENGLISH

NCIC CTG Trial: **BL.12**

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain EQ-5D Questionnaire- please check (✓)

☐ Prior to randomization

During chemotherapy:

☐ Days 5 - 7 cycle 1 ☐ Days 5 - 7 cycle 2 ☐ Day 1 cycle 4 ☐ Day 1 cycle 8 ☐ Day 1 cycle 12

☐ Day 1 cycle 16 ☐ Day 1 cycle 20 ☐ Day 1 cycle 24 ☐ Day 1 cycle 28 ☐ Day 1 cycle _____

Off Treatment:

☐ week 6

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ___ ___ ___

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

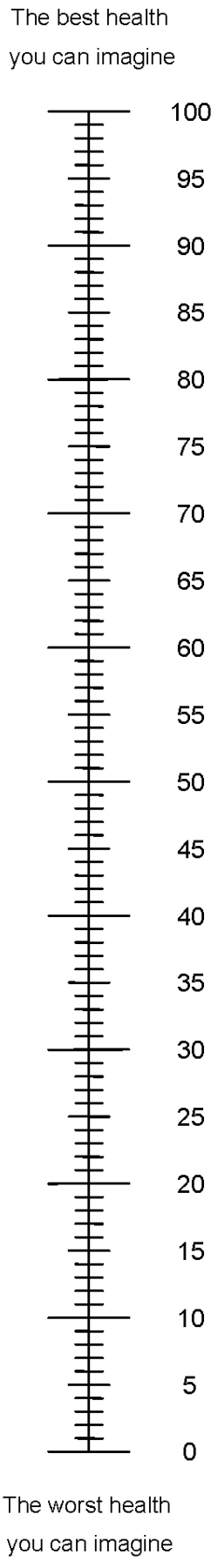
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



LIST OF CONTACTS

PATIENT REGISTRATION

All patients must be registered as described in Section 7.1 before any treatment is given.

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST (Baseline Form). Must be completed prior to registration. Starting doses will also be calculated at registration.	Susan McEathron Clinical Trials Assistant NCIC CTG Email: smceathron@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on NCIC CTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Gail McDonald Study Coordinator NCIC CTG Email: gmcdonald@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator NCIC CTG Email: wparulekar@ctg.queensu.ca		
STUDY CHAIR	Dr. Srikala Sridhar Study Chair Email: srikala.sridhar@uhn.ca	416-946-4501 (x2520)	416-946-6546
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator NCIC CTG or Gail McDonald Study Coordinator NCIC CTG	613-533-6430	613-533-2941
DRUG ORDERING	See Appendix III and trial website for full details and contact information		

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

August 18, 2017

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								
	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	.**