Protocol Title:

A Phase II, Single Arm, Open-Label, Multi-Center, Safety and Tolerability Trial with *nab*-Paclitaxel (Abraxane®) Plus Carboplatin Followed by *nab*-Paclitaxel Monotherapy as First-Line Treatment For Subjects With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and an Eastern Cooperative Oncology Group Performance Status of 2 (Abound.PS 2).

NCT Number: NCT02289456

Original Protocol Date: 12 January 2015

DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

ABI-007-NSCL-004

A PHASE II, SINGLE ARM, OPEN-LABEL, MULTI-CENTER, SAFETY AND TOLERABILITY TRIAL WITH *nab*-PACLITAXEL (ABRAXANE®) PLUS CARBOPLATIN FOLLOWED BY *nab*-PACLITAXEL MONOTHERAPY AS FIRSTLINE TREATMENT FOR SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) AND AN EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS OF 2 (ABOUND.PS 2)

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(ABOUND.PS2)

INVESTIGATIONAL PRODUCT:	***nab*-Paclitaxel (Abraxane®)**
PROTOCOL NUMBER:	**ABI-007-NSCL-004**
ORIGINAL DATE FINAL:	**11 August 2014**
AMENDMENT 1 DATE FINAL:	**12 January 2015**
EudraCT NUMBER:	**Not applicable**
IND NUMBER:	**114882**
SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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PROTOCOL SUMMARY

Study Title

A Phase II, Single Arm, Open-Label, Multi-Center, Safety and Tolerability Trial with *nab*-Paclitaxel (Abraxane®) Plus Carboplatin Followed by *nab*-Paclitaxel Monotherapy as First-Line Treatment For Subjects With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and an Eastern Cooperative Oncology Group Performance Status of 2 (Abound.PS 2).

Indication

First-line treatment of subjects with locally advanced or metastatic NSCLC and an Eastern Cooperative Oncology Group Performance Status 2 (ECOG PS 2).

Objectives

Primary

- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.

Secondary

- To evaluate the efficacy (progresstion-free survival [PFS], disease control rate [DCR], overall survival [OS] and overall response rate [ORR]) of the *nab*-paclitaxel and carboplatin combination dosing regimen, followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.
- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.

Exploratory

- To assess healthcare resource utilization
- To assess co-morbidity status using the Charlson Co-Morbidity Index (CCI)
- To assess quality of life
- To explore the correlation between the physician- and patient-evaluated Eastern Cooperative Oncology Group Performance Status
- To explore the correlation between the physician- and patient-evaluated Karnofsky Performance Status
- To assess the safety and efficacy of continuous treatment with *nab*-paclitaxel as monotherapy after 4 cycles of *nab*-paclitaxel in combination with carboplatin

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Study Design

Approximately 50 subjects with stage IIIB or IV NSCLC and ECOG PS 2 will be enrolled in the study to receive *nab*-paclitaxel plus carboplatin for 4 cycles, followed by monotherapy with *nab*-paclitaxel in the absence of disease progression.

The study will consist of a 28-day screening period, induction with 4 cycles of *nab*-paclitaxel and carboplatin followed by *nab*-paclitaxel monotherapy, and follow-up. The screening period for eligibility determination begins upon subject written informed consent.

Induction Part

Approximately 50 eligible subjects will be enrolled in the study. In the induction part subjects will receive 4 cycles of *nab*-paclitaxel plus carboplatin, provided all eligibility criteria are met within a 28-day screening period prior to Cycle 1 Day 1.

Induction treatment will consist of:

- *nab*-Paclitaxel 100 mg/m^2 intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle
- Carboplatin area under the curve (AUC) = 5 mg*min/mL IV on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel infusion.

Monotherapy Part

Subjects may continue in the study and receive monotherapy with *nab*-paclitaxel in the absence of disease progression, after the completion of 4 cycles of the induction therapy. They will receive:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle.

Tumor evaluations will be assessed by the investigative sites and response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 (Eisenhauer, 2009).

Follow-up Period

All subjects who discontinue treatment for any reason other than lost to follow-up or death, will enter the follow-up period. All subjects will continue to have computed tomography (CT) scans in accordance with their institution's standard of care and the findings will be reported on the appropriate electronic Case Report Form (eCRF) pages. In addition, all post-treatment anti-cancer therapy will be reported on the appropriate eCRF pages. Minimally, all subjects will be followed for overall survival (OS) every 90 days by phone contact or chart review for documentation of last contact for up to 1 year after the last subject is enrolled.

Study Population

Adults ≥ 18 years old with locally advanced or metastatic NSCLC and PS 2 who have not received chemotherapy for their advanced disease and are not candidates for curative surgery or radiation therapy, will be eligible for this study. The study will enroll approximately 50 subjects.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Length of Study

Enrollment will last approximately 15 months. The total length of this phase 2 study with induction, monotherapy and follow-up is estimated at approximately 27 months.

The End of Trial is defined as either the date of the last visit of the last subject, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

***nab*-Paclitaxel**

nab-Paclitaxel is designated as investigational product throughout the trial and will be packaged and supplied by Celgene Corporation. The preparation for IV administration procedures for investigational product should be followed as per the approved local prescribing information.

Carboplatin

Carboplatin will be provided commercially, by prescription only. The preparation for IV administration procedures for carboplatin should be followed as per the approved local prescribing information.

Overview of Statistical Methods

Approximately 50 subjects will be enrolled and treated in this study. Enrollment will be conducted and tracked centrally using an Interactive Response Technology (IRT) system. The date of enrollment is defined as the date on which the subject is registered into the IRT system.

All evaluations of the safety and efficacy endpoints will be based on the point estimates and the associated two-sided 95% confidence intervals (CI).

Overview of Safety Assessments

The treated population, which includes all subjects who received at least one dose of investigational product, will be the analysis population for all safety analyses.

The primary endpoint for the study is the percentage of subjects who discontinue during the induction part due to treatment-emergent adverse events (TEAEs).

Treatment-emergent adverse events are defined as any adverse event (AE) or serious adverse event (SAE) occurring or worsening on or after the first dose of the investigational product through 28 days after the last dose of investigational product. In addition, any SAE with an onset date more than 28 days after the last dose of investigational product that is assessed by the Investigator as related to investigational product will be considered a TEAE. The TEAE rate will be summarized by descriptive statistics with the corresponding 95% confidence interval.

In addition to the primary safety endpoint described above which focuses on the safety and tolerability of the induction regimen in subjects with performance status 2, the safety and tolerability of the treatment regimen for the entire study will be assessed by TEAE rate, Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction, dose delay, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death for the entire

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

study will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

Overview of Efficacy Assessments

The treated population, which includes all subjects who received at least one dose of investigational product, will be used for all efficacy analyses.

Progression-free survival, DCR, ORR, and OS over the entire study are the key efficacy endpoints of the study.

Progression-free survival is defined as the time from the date of first dose of investigational product to the date of disease progression or death (from any cause) on or prior to the data cutoff date for analyses, whichever occurs first, based on the Investigator's assessment of the data from CT scans using RECIST v1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of investigational product.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time and PFS rates at regular intervals from the first day of investigational product treatment (including two-sided 95% confidence interval [CI]).

Disease control rate (percent of subjects who have continued stable disease, complete or partial response), and overall response rate (percent of subjects who have a radiologic complete or partial response), as evaluated by the Investigator based on the RECIST v1.1 guidelines, will be estimated along with the associated 2-sided 95% CIs.

Overall survival will be summarized by descriptive statistics with the associated 95% CIs, as described for PFS.

The primary analysis of both the safety and efficacy endpoints will be performed at approximately 6 months after the last subject is enrolled. Subjects will be followed for OS until 1 year after the last subject is enrolled.

Sample Size

The primary objective of the study is to assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination treatment regimen in the study population. All evaluations of the safety and efficacy endpoints will be based on the point estimates and the associated two-sided 95% confidence intervals rather than formal inferential statistical tests.

The primary endpoint of the study is the percentage of subjects who discontinue during the induction part due to TEAEs. With a sample size of 50, the maximum width of the 95% confidence interval for any proportion is 28.9%. Of note, assuming the underlying percentage of subjects who will discontinue from study treatment due to TEAEs is 30%, a sample size of 50 provides 80% power, with a one-sided significance level of 10%, to detect an increase of 15 percentage points from 30%.

Scientific Steering Committee

An external Scientific Steering Committee (SSC) will be established, with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. A charter will be established for regular safety data review. The SSC will have the ability to recommend termination of the study if a safety signal is discovered.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Final recommendations of the SSC will reflect the judgment of the SSC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the SSC will be made by the Sponsor.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

TABLE OF CONTENTS

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

LIST OF TABLES

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

LIST OF FIGURES

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

1. INTRODUCTION

1.1. Treatment of Advanced Stage Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related deaths among men and women worldwide, with 1.2 million new cases diagnosed each year. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% of all new cases. There are an estimated 1.1 million lives lost per year (approximately 500,000 in the United States [US] and European Union [EU] alone) due to NSCLC. Smoking is the causative factor for up to 85% of cases (Global Lung Cancer Coalition, 2015).

The majority of patients are not diagnosed until the tumor has progressed beyond the primary site. Despite several advances in patient selection, development of targeted agents and optimization of chemotherapy regimens, the majority of patients with advanced NSCLC continue to have an unmet medical need (Schiller, 2013).

Platinum-containing chemotherapy doublet regimens remain the standard first-line treatment in the majority of patients, in the US and Japan. Similarly, in the EU, a third-generation chemotherapeutic agent (docetaxel, gemcitabine, paclitaxel, or vinorelbine), most commonly gemcitabine or vinorelbine, plus a platinum drug is used for advanced NSCLC (National Institute for Health & Clinical Excellence [NICE], 2011). In recent years, NSCLC treatment decisions are being determined based on tumor histology (squamous versus non-squamous), or based on molecular characteristics of the tumor for the use of agents targeting specific receptor kinases involved in oncogenic signaling pathways (eg, epidermal growth factor receptor [EGFR], echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

In advanced NSCLC, the combination of paclitaxel/carboplatin results in modest response rate, survival, and toxicity. Paclitaxel is currently available in the proprietary product Taxol® (paclitaxel) Injection, manufactured by Bristol-Myers Squibb (New York, NY) and by several other generic drug manufacturers. Taxol consists of paclitaxel dissolved in a proprietary solvent, Cremophor® EL (BASF, Ludwigshafen, Germany), and ethanol. While this solvent system addresses the poor water solubility of paclitaxel, the Taxol formulation has a number of other limitations. For example, Taxol administration requires routine premedication with corticosteroids, diphenhydramine, and histamine H2 receptor antagonists to reduce the incidence of hypersensitivity reactions and histamine release caused by a response to the formulation vehicle (Gelderblom, 2001; Lorenz, 1977; Weiss, 1990). Furthermore, the solvent alters drug pharmacokinetics (PK), leading to highly increased systemic drug exposure, decreased drug clearance, nonlinear PK, and lack of dose-dependent antitumor activity (Sparreboom, 1999; ten Tije, 2003; van Tellingen, 1999). Also, Taxol must be administered over a period of either 3 hours or 24 hours.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

nab-Paclitaxel approval in first-line locally advanced or metastatic NSCLC:

nab-Paclitaxel for Injectable Suspension is approved for the treatment of metastatic breast cancer (globally) and for the treatment of adenocarcinoma of the pancreas (US). For NSCLC, *nab*-paclitaxel is approved in the US in combination with carboplatin for first-line treatment of patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or radiation therapy. Compared with paclitaxel, *nab*-paclitaxel exhibits 10-fold higher mean C_{max} of free paclitaxel, delivers 33% higher drug concentration to tumors in preclinical xenograft models, and demonstrates enhanced transport across endothelial cell monolayers (Desai, 2006; Gardner, 2008). The Cremophor EL-free medium enables *nab*-paclitaxel to be given over a shorter duration without the need for steroid premedication to prevent solvent-related hypersensitivity reactions. The recommended dose of *nab*-paclitaxel for the NSCLC indication is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.

The Food and Drug Administration (FDA) approval of *nab*-paclitaxel in combination with carboplatin was based on the evaluation of phase 1 and 2 data (Belani, 2008; Rizvi, 2008; Socinski, 2010), as well as the pivotal phase 3 study (CA031). The pivotal phase 3 study was a multicenter, randomized, open-label study conducted in 1052 chemo-naive subjects with Stage IIIB/IV non-small cell lung cancer to compare *nab*-paclitaxel in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. This study enrolled patients that were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or PS 1 only. *nab*-Paclitaxel was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of area under the curve (AUC) = 6 mg*min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel/paclitaxel infusion. Treatment was administered until disease progression, development of an unacceptable toxicity or patient withdrawal. The primary efficacy outcome measure was overall response rate (ORR) as determined by a central independent review committee using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.0). In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were white, 49% had carcinoma/adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, 15% were ≥70 years of age and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms. Patients in the *nab*-paclitaxel/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm (33% versus 25%).

Non-inferiority analysis of overall survival (OS) demonstrated that *nab*-paclitaxel/carboplatin (*nab*-p/C) treatment is not inferior to paclitaxel/carboplatin (P/C) treatment. Median overall survival in the *nab*-paclitaxel arm was 12.1 months versus 11.2 months in the control arm (p = 0.271; hazard ratio [HR] = 0.922, 95% confidence interval [CI], 0.797 to 1.066; p = .271). There was an approximately 10% improvement in progression-free survival (median, 6.3 v 5.8 months; HR, 0.902; 95% CI, 0.767 to 1.060; p = .214) in the *nab*-paclitaxel arm versus the P/C arm.

Adverse events (AEs) were assessed in 514 *nab*-paclitaxel/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients. The following common (≥ 10% incidence) AEs

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

were observed at a similar incidence in *nab*-paclitaxel/carboplatin and paclitaxel/carboplatin arms: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the *nab*-paclitaxel plus carboplatin treatment group). Toxicities, particularly neuropathy and Grade 3-4 neutropenia were less pronounced using *nab*-paclitaxel in the dose and schedule employed. Laboratory-detected abnormalities which occurred with a difference ≥ 5% for *nab*-paclitaxel plus carboplatin vs paclitaxel injection plus carboplatin grade 3-4 were: anemia 28% vs 7%, neutropenia 47% vs 58% and thrombocytopenia 18% vs 9%.

Per protocol, patients were stratified by NSCLC histology (squamous cell carcinoma vs adenocarcinoma vs other histology). Subgroup analyses were performed to assess the influence of squamous vs non-squamous histology on the primary efficacy endpoint of overall response rate (the percentage of patients who achieved an objective confirmed complete response (CR) or partial response (PR) based on the blinded radiological review using RECIST response guidelines, Version 1.0). The proportion of patients with squamous cell carcinoma who responded was significantly higher for the ABI-007/carboplatin regimen relative to the Taxol/carboplatin regimen (41% vs 24%: p_A/p_T: 1.680; $p < 0.001$). The proportion of patients with non-squamous cell carcinoma with a confirmed complete or partial overall response was comparable between the ABI-007 and Taxol/carboplatin arms (26% vs 25%: p_A/p_T: 1.034; $p = 0.808$).

Table 1: Blinded Radiology Assessment of Overall Response Rate (Intent-to-treat Population)

Variable Category/Statistic	*nab*-Paclitaxel/ carboplatin (N=521)	Paclitaxel/ carboplatin (N=531)	Response Rate Ratio (p_A/p_T)	p-value
Patients with Confirmed Complete or Partial Overall Response				
n (%)	170 (33%)	132 (25%)	1.313	0.005*
Confidence Interval (CI) [a]	28.6, 36.7	21.2, 28.5	1.082, 1.593	
Complete Response, n (%)	0	1 (< 1%)		
Partial Response, n (%)	170 (33%)	131 (25%)		

P_A/PT: response rate of *nab*-paclitaxel/response rate of paclitaxel.
[a] 95% CI of response rate and 95.1% CI of response rate ratio.
* Indicates p-value < 0.049.
Note: p-value is based on a chi-square test.
Source: Data on File.

1.2. Treatment of Patients with Advanced Stage NSCLC and Poor Performance Status (PS)

The functional status of patients with NSCLC is commonly assessed by two widely used measures of PS; the ECOG Scale (Oken, 1982) and the Karnofsky Performance Scale (Karnofsky, 1948). These scales equate variables such as the ability to carry out normal daily activities, the proportion of waking hours a patient is ambulatory, and symptom burden, to a

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

numerical value of PS. Despite the general subjectivity of PS assessment, and the multiple contributing factors, PS is an important prognostic factor for survival in patients with NSCLC upon which treatment decisions are commonly made (Kelly, 2004). Patients with a borderline or poor performance status (ie, ECOG PS ≥ 2) comprise about 30 to 40 percent of patients with NSCLC (Lilenbaum, 2008).

The majority of research in advanced non-small cell lung cancer (NSCLC) has generally focused on patients with good performance status (ECOG PS 0-1). However, a significant proportion of patients with advanced NSCLC have ECOG PS 2, either due to bulky disease or related to medical co-morbidities. Treatment of ECOG PS 2 patients varies, due to concerns regarding treatment-related toxicities, rapid deterioration of performance status and poor overall survival relative to patients with ECOG PS 0-1, and thus there is a high unmet need which warrants further clinical research in this patient population. Patients with ECOG PS 2 have a worse prognosis than those with PS 0-1 with median overall survival (OS) of 36 and 26 weeks respectively versus 10 weeks for PS 2 patients (Hoang, 2005).

The potential toxicity of cytotoxic chemotherapy can pose special concerns in poor performance status patients with advanced NSCLC, and thus earlier treatment guidelines lacked consensus on specific treatment recommendations, particularly with respect to single-agent versus combination chemotherapy. A randomized phase 2 trial of paclitaxel plus carboplatin or gemcitabine plus cisplatin in ECOG PS 2, NSCLC enrolled 103 patients, all histologies (ECOG 1599). The one year OS rates were 4.2 months for gemcitabine plus cisplatin versus 6.2 months in paclitaxel and carboplatin. The median number of cycles administered per arm was 3 cycles. The results suggest that platinum-based combination chemotherapy for PS 2 patients with NSCLC is feasible with acceptable toxicity, but survival remains inferior to that of PS 0-1 patients (Langer, 2007).

Furthermore, the combined data from the STELLAR 3 and 4 studies provided important retrospective analyses of the potential efficacy and tolerability of paclitaxel-carboplatin relative to single-agent chemotherapy (Lilenbaum, 2009). The hypothesis that PS 2 patients could benefit from platinum-doublet chemotherapy were supported prospectively in a phase 3 study of pemetrexed-carboplatin vs pemetrexed (Zukin 2013); in this trial, combination chemotherapy resulted in superior outcomes of ORR (23.8 % vs 10.3%, $p = 0.032$), progression-free survival (PFS) (5.8 months vs 2.8 months, HR 0.46, $p < 0.001$) and OS (9.3 months vs 5.3 months, HR 0.62, $p = 0.001$).

1.3. Rationale For Schedule and Dosage Selection

Patients with NSCLC and an ECOG PS 2 are at risk of more toxicities, lower response rates and shorter survival times than healthier patients, when treated with standard chemotherapy. This is due in large part to disease burden and co-morbidities. Therefore dosage and schedule selection is critical in order to balance toxicities while optimizing treatment benefit. Recent phase 3 trials demonstrated that platinum-doublet chemotherapy can provide substantial clinical benefits, including improved overall survival, for older patients and those with ECOG PS 2 (Lilenbaum, 2008).

The dose of carboplatin AUC 5 (though less than the standard dose of AUC 6 used in the PS 0-1 setting) is chosen for this PS 2 protocol, based upon the efficacy and tolerability results from the Randomized Phase III Trial of Single-Agent Pemetrexed Versus Carboplatin and Pemetrexed in

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Patients With Advanced Non–Small-Cell Lung Cancer and Eastern Cooperative Oncology Group Performance Status of 2.

In the phase 3 trial, standard dose of pemetrexed (500mg/m^2) was administered in both arms, however, carboplatin AUC 5 was administered in the combination arm. The reduced carboplatin dose of AUC 5 alleviated the toxicity burden of the combination chemotherapy, whereby the Grade 3 and 4 AE profile was only marginally worse in the carboplatin-pemetrexed arm. However, only 53.9% of patients completed 4 cycles of treatment, compared to 70.9% of patients in the carboplatin- pemetrexed arm. The principal reasons for discontinuation in the pemetrexed and combination arms included early death (14.7% versus 9.7%), early progression (15.7% versus 7.8%), clinical deterioration (12.7% versus 6.8%), toxicity (0% versus 1.9%) and others (4% versus 2%), respectively. As expected therapy delays (20.6% versus 44.7%) and dose reductions (2.9% versus 3.9%) were more common in the combination arm (Zukin 2013).

The dose for *nab*-paclitaxel in this protocol will be in accordance with the current approved label in NSCLC, however, the schedule for *nab*-paclitaxel will be modified to include only Days 1 and 8 every 21 days. The day 15 dose will be omitted to minimize toxicities. This dose/schedule had been investigated in a phase 2 trial of carboplatin AUC5 and *nab*-paclitaxel 100mg/m^2 days 1 and 8 every 21 days in locally advanced Stage III NSCLC patients with PS 2 . During this phase 2 study, the preliminary toxicity profile of continuous weekly dosing of *nab*-paclitaxel resulted in Grade 3/4 neutropenia that necessitated day 15 dose omission, leading to a protocol amendment. Nevertheless, this modified schedule was shown to be feasible with manageable side-effects and encouraging efficacy (ORR 67%, median PFS 11 months and median OS 17 months). Therefore, this proposed protocol aims to build on the data from prior studies in PS 2 patients, ie, slightly lower dose-intensity of combination chemotherapy provides a tolerable toxicity profile while maintaining reasonable efficacy outcomes. After 4 cycles of *nab*-paclitaxel and carboplatin, patients will have the option of continuing on *nab*-paclitaxel monotherapy, which will have the potential of being better tolerated than the chemotherapy doublet. This will also allow us to evaluate efficacy and safety for use of *nab*-paclitaxel as a continuous maintenance treatment.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.

2.2. Secondary Objectives

- To evaluate the efficacy (PFS, DCR, OS and ORR) of the *nab*-paclitaxel and carboplatin combination dosing regimen, followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.
- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen, followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess healthcare resource utilization
- To assess co-morbidity status using the Charlson Co-Morbidity Index (CCI)
- To assess quality of life
- To explore the correlation between the physician- and patient-evaluated ECOG PS
- To explore the correlation between the physician- and patient-evaluated Karnofsky performance status (KPS) at baseline
- To assess the safety and efficacy of continuous treatment with *nab*-paclitaxel as monotherapy after 4 cycles of *nab*-paclitaxel in combination with carboplatin

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

3. STUDY ENDPOINTS

3.1. Primary Endpoint

3.1.1. Safety

- Percentage of subjects who discontinue study treatment during the induction part due to treatment emergent AEs (TEAEs).

3.2. Secondary Endpoint(s)

The secondary endpoints listed below will be evaluated across the induction and monotherapy parts.

3.2.1. Safety

- The type, frequency, and severity of AEs and serious adverse events (SAEs) graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0)
- Discontinuation rate
- The dose intensity
- The incidence of dose reduction

3.2.2. Efficacy

- Progression free survival
- Disease control rate
- Overall survival
- Overall response rate

3.3. Exploratory Endpoint(s)

The exploratory endpoints listed below will be evaluated across the induction and monotherapy parts, unless indicated otherwise.

3.3.1. Exploratory Endpoints

- Healthcare resource utilization throughout the study using a questionnaire
- Changes in Physician-Reported ECOG PS
- Changes in the EuroQol-5D (EQ5D-5L) and Lung Cancer Symptom Score (LCSS)
- Summary of the Charlson Co-Morbidity Index (CCI) at baseline
- Correlation between Subject-Reported ECOG PS and Physician-Reported ECOG PS during the treatment period

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

- Correlation between Subject-Reported KPS and Physician-Reported KPS at baseline

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

4. OVERALL STUDY DESIGN

4.1. Study Design

Approximately 50 subjects with stage IIIB or IV NSCLC and ECOG PS 2 will be enrolled in the study to receive *nab*-paclitaxel plus carboplatin for 4 cycles, followed by monotherapy with *nab*-paclitaxel in the absence of disease progression.

The study will consist of a 28-day screening period, induction with 4 cycles of *nab*-paclitaxel and carboplatin followed by *nab*-paclitaxel monotherapy, and follow-up.

The screening period for eligibility determination begins upon subject written informed consent.

Induction Part

Approximately 50 eligible subjects will be enrolled in the study. In the induction part subjects will receive 4 cycles of *nab*-paclitaxel plus carboplatin, provided all eligibility criteria are met within a 28-day screening period prior to Cycle 1 Day 1.

Induction treatment will consist of:

- *nab*-Paclitaxel 100 mg/m^2 intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle
- Carboplatin AUC = 5 mg*min/mL IV on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel infusion.

Monotherapy Part

Subjects may continue in the study and receive monotherapy with *nab*-paclitaxel in the absence of disease progression, after the completion of 4 cycles of the induction therapy. They will receive:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle.

Tumor evaluations will be assessed by the investigative sites and response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 (Eisenhauer, 2009).

Follow-up Period

All subjects who discontinue treatment for any reason other than lost to follow-up or death, will enter the follow-up period. All subjects will continue to have computed tomography (CT) scans in accordance with their institution's standard of care and the findings will be reported on the appropriate electronic Case Report Form (eCRF) pages. In addition, all post-treatment anti-cancer therapy will be reported on the appropriate eCRF pages. Minimally, all subjects will be followed for overall survival (OS) every 90 days by phone contact or chart review for documentation of last contact for up to 1 year after the last subject is enrolled.

4.2. Study Design Rationale

nab-Paclitaxel demonstrated clinically meaningful benefit when studied in a phase 3 comparative study evaluating the use of carboplatin with either *nab*-paclitaxel (100 mg/m^2 weekly) or

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

paclitaxel (200 mg/m^2 every 3 weeks) in the first-line treatment of advanced stage NSCLC patients with PS of 0-1. A higher response rate was demonstrated for the *nab*-paclitaxel - carboplatin arm (33%) compared to the paclitaxel-carboplatin arm (25%), $p = 0.005$ (Socinski, 2012). There was an approximate 8% difference in PFS and OS between the study arms (non-statistically significant) favoring *nab*-paclitaxel. In subgroup analyses, NSCLC subjects with squamous histology and elderly subjects (≥ 75 years of age) were observed to have experienced particularly robust clinical benefit. The most common treatment-related Grade 3 or 4 hematologic adverse events included neutropenia, leucopenia, anemia, and thrombocytopenia. The most common treatment-related Grade 3 or 4 non-hematologic adverse events were fatigue, sensory neuropathy, anorexia, nausea, myalgia and arthralgia. *nab*-Paclitaxel plus carboplatin was associated with significantly lower rates of Grade 3 and 4 sensory neuropathy, arthralgia, myalgia and neutropenia, but higher rates of anemia and thrombocytopenia.

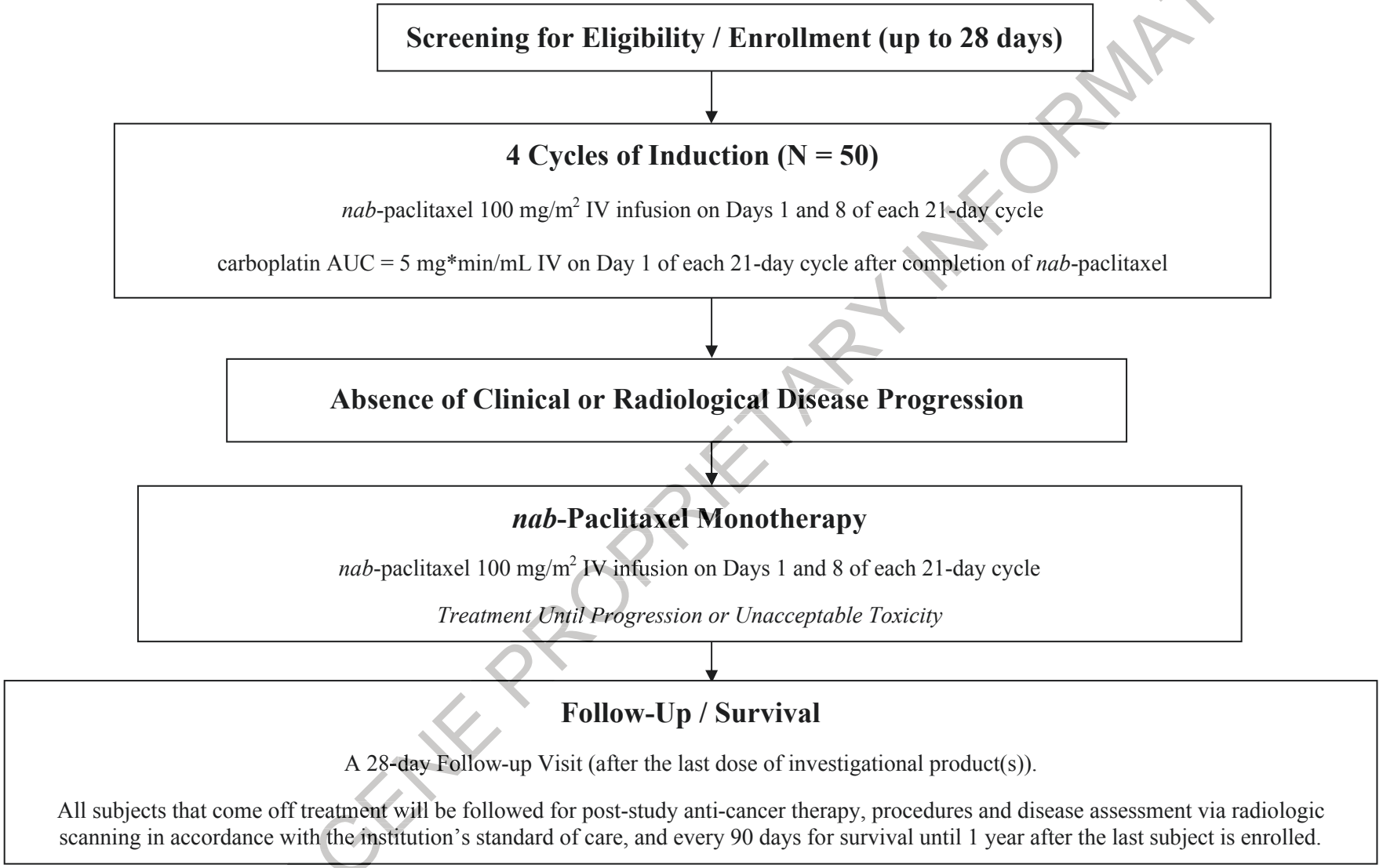
The treatment landscape for PS 2 patients can include single-agents or platinum-based doublets as reasonable options (National Comprehensive Cancer Network [NCCN] 2014). So far there is no compelling data from clinical trials which shows superiority of one doublet regimen over another and there is no consensus on specific treatment recommendations for PS 2 patients. There is limited data of carboplatin plus *nab*-paclitaxel in the locally advanced or metastatic NSCLC setting for patient with PS 2 status. Nevertheless, the encouraging results from a phase 2 study in Stage III NSCLC patients provides important insight that PS 2 patients can benefit from the combination of carboplatin and *nab*-paclitaxel, albeit with slight modification to the regimen. Therefore, to further characterize the tolerability and efficacy of this modified regimen in PS 2 NSCLC patients in the locally advanced/metastatic setting, this open-label, single-arm study is proposed.

The role of continued maintenance chemotherapy has been demonstrated in several phase 3 trials, eg, pemetrexed, gemcitabine, docetaxel and bevacizumab; albeit with varied toxicity and efficacy outcomes. However, the impact of continued maintenance therapy in prolonging tumor response or stable disease for PS 2 NSCLC patients remains to be elucidated. Consequently, this study provides a unique opportunity to evaluate the impact of continuing *nab*-paclitaxel as maintenance chemotherapy after 4 cycles of induction, at the discretion of the treating Investigator's benefit:risk assessment.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Figure 1: Overall Study Design



CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

4.3. Study Duration

4.3.1. Duration of Treatment

All subjects will be treated until disease progression, unacceptable toxicity, death, lost to follow-up or physician and/or patient decision to discontinue treatment.

Enrollment will last approximately 15 months. The total length of this phase 2 study with induction, monotherapy, and follow-up is estimated at approximately 27 months, including a 1 year follow-up from the last patient enrolled in the study.

4.4. End of Trial

The end of trial is defined as either the date of the last visit of the last subject, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the later date.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

5. TABLE OF EVENTS

Table 2: Table of Events - Induction

Assessment	Screening/ Baseline	CYCLES 1 To 4 (21-days)		Post Every 2 Cycles of Treatment (-3/+7 days)	Treatment Discontinuation	28-day Follow up visit	Follow-up/ Survival[l]
	Day -28 to Day 1	Day 1 (±2 days)	Day 8 (±2 days)				
Informed Consent	X	-	-	-	-	-	-
Medical History, Prior Medication and Procedures[a]	X	-	-	-	-	-	-
Serum β-hCG[b]	X	-	-	-	-	-	-
Complete Chest CT Scan (including adrenal glands) with and without contrast and any other studies required for tumor imaging[c]	X	-	-	X	X	-	X
Height and Weight[d]	X	X	X	-	-	-	-
Body Surface Area (BSA) Calculation[e]	X	X	X	-	-	-	-
Physician-Reported ECOG PS	X	X	-	-	X	-	-
Concomitant Medication/Procedures[f]	-	X	X	-	X	X	X
Histology and Mutation Status	X	-	-	-	-	-	-
Hematology and Serum Chemistry[g]	X	X	X	-	X	X	-
Adverse Event Evaluation	X	X	X	-	X	X	-
nab-paclitaxel Administration	-	X	X	-	-	-	-
Carboplatin Administration	-	X	-	-	-	-	-
Electrocardiogram (ECG)	X	-	-	-	-	-	-
Baseline TNM Stage	X	-	-	-	-	-	-
Charlson Co-morbidity Index	X	-	-	-	-	-	-

CELGENE PROPRIETARY INFORMATION

Table 2: Table of Events - Induction (Continued)

Assessment	Screening/ Baseline	CYCLE 1 to 4 (21-days)		Post Every 2 Cycles of Treatment (-3/+7 days)	Treatment Discontinuation	28-day Follow-up visit	Follow-up/ Survival[l]
	Day -28 to Day 1	Day 1 (±2 days)	Day 8 (±2 days)				
CT Scan of Head or Brain Magnetic Resonance Imaging (MRI), bone scan (X-rays if needed)[h]	X	-	-	-	-	-	-
Physical Examination[i]	X	-	-	-	X	-	-
Vital Signs[i]	X	-	-	-	X	-	-
Smoking History	X	-	-	-	-	-	-
Spirometry and Pulse Oximetry[j]	X	X	-	-	X	X	-
Calculated Creatinine Clearance (24-hour urine collection)[k]	X	X	-	-	-	X	-
Healthcare Resource Utilization Questionnaire	-	X	-	-	X	X	-
Subject-Reported ECOG PS	-	X	-	-	X	-	-
Subject- and Physician-Reported KPS	-	X	-	-	-	-	-
LCSS and EQ5D-5L	-	X	-	-	X	-	-
Subjects Weight 6 Months Prior to signing the ICF for nutritional status assessment	X	-	-	-	-	-	-
Reversibility of PS 2 Status[m]	X	-	-	-	-	-	-
Survival Phone Call (or chart review for documentation of last contact)	-	-	-	-	-	-	X

ALT: alanine transaminase, ANC: absolute neutrophil count, AST: aspartate transaminase, beta hCG: beta human chorionic gonadotropin, CT: Computed Tomography, ECOG: Eastern Cooperative Oncology Group, eCRF: electronic case report form, EQ5D-5L: EuroQol-5D, ICF: Informed Consent Form, KPS: Karnofsky Performance Status: LCSS: Lung Cancer Symptom Score, NSCLC: non-small cell lung cancer, PS: Performance status, RECIST: Response Evaluation Criteria in Solid Tumors, TNM: tumor, node and metastasis, WBC = white blood cell

[a] Significant prior medications and procedures; provided and or performed within 28 days of signing the ICF will be recorded. All NSCLC-related prior medications/procedures/prior radiation therapy will be recorded regardless of time.

[b] A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a Serum β-hCG pregnancy test must be performed to assess eligibility at screening within 72 hours of the first administration of investigational product.

[c] All subjects must have measurable disease via objective scanning as defined by the RECIST v1.1 criteria. Required is a complete chest CT scan (including base of neck and adrenal glands) with and without contrast, unless contraindicated, to be performed at screening. Scans will be performed after every 2 cycles of treatment and at treatment

CELGENE PROPRIETARY INFORMATION

discontinuation. The method of assessment utilized at baseline will remain consistent throughout study duration. A complete chest CT scan will be performed at each protocol required time point regardless of the location of the baseline disease. Scans will be archived as per institution standards.

[d] Height is only measured at baseline and will be recorded on the appropriate eCRF page. Weight will be measured at baseline and every visit, before drug administration and recorded on the appropriate eCRF page.

[e] BSA will be calculated at screening and recalculated if body weight changes by more than 10% since baseline, or since the previous visit when BSA was last recalculated and recorded in the subject's medical record only. BSA and body mass index will be a derived value, using the height, and weights reported.

[f] All concomitant medications and procedures associated with serious adverse events (SAEs) will be recorded on the eCRF from the time of signing the ICF through 28-days post last dose of investigational product(s). Reporting of concomitant medications and procedures associated with non-SAEs will include all cancer-related procedures, analgesics, steroids, transfusions, growth factors, bisphosphonates, denosumab, and antibiotics. All treatments and procedures provided as part of best supportive care (BSC) will require reporting on the eCRFs. During the follow-up period, post-study anti-cancer therapy and procedures will be collected and reported on the appropriate eCRF.

[g] Local laboratory assessments will be done prior to each *nab*-paclitaxel treatment during the study and as clinically indicated. Note: the Cycle 1 Day 1 hematology and serum chemistry will not require repeating if the screening hematology and serum chemistry were performed within 2 days of the Cycle 1Day 1 visit. ANC, WBC, platelet count, AST/serum glutamic oxaloacetic transaminase, ALT/serum glutamic pyruvic transaminase, albumin, serum creatinine, total bilirubin, and hemoglobin (Hgb) results will be collected routinely on the appropriate eCRF pages. All other routine laboratory test data will not be collected in the eCRF unless it is clinically significant, which will then be reported as an AE, and the specific associated laboratory parameter(s) will be recorded on the laboratory assessments eCRF.

[h] CT Scan of Head or Brain Magnetic Resonance Imaging (MRI) and Bone Scan (X-rays if needed) will be performed ONLY if deemed appropriate by the treating physician.

[i] Physical exam and vital signs data will not be captured in the eCRFs unless deemed clinically significant by the treating physician, in which case the event will be captured as an adverse event. At screening, findings deemed clinically significant will be captured as medical history.

[j] Spirometry will be measured using an FDA approved, portable spirometer. The following values will be measured and reported on the appropriate eCRF page: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF). In addition pulse oximetry will be used to measure the saturation of peripheral oxygen (sPO_2). These data will be reported on the appropriate eCRF page.

[k] Creatinine clearance (CrCl) will be calculated (if renal impairment is suspected 24-hour urine collection for measurement is required – but only at baseline), and these data will be collected on the eCRFs.

[l] All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up or death, will enter follow-up. It will consist of one visit 28 days after the last dose of investigational product(s). Thereafter subjects will return to the clinic for objective scanning per the institution's policy and collection of post study anti-cancer therapy. In addition, at minimum, subjects will be contacted by phone for survival status, approximately every 90 days (+/- 14 days). Survival status can also be gleaned from clinic visits / records. All data will be reported on the appropriate eCRF for up to 1 year after the last subject is enrolled.

[m] The treating oncologist will use his/her best clinical judgment to predict if treatment with the protocol regimen could improve poor PS of the patient, see Appendix B for more details.

CELGENE PROPRIETARY INFORMATION

Table 3: Table of Events – Monotherapy

Assessment	EVERY CYCLE (21-days)		Post Every 2 Cycles of Treatment (-3/+7 days)	Treatment Discontinuation	28-day Follow-up Visit	Follow-up/Survival[i]
	Day 1 (±2 days)	Day 8 (±2 days)				
Complete Chest CT Scan (including adrenal glands) with or without contrast and any other studies required for tumor imaging[a]	-	-	X	X	-	X
CT Scan of Head or Brain Magnetic Resonance Imaging (MRI) and Bone Scan (X-rays if needed)[b]	-	-	X	X	-	X
Weight[c]	X	X	-	-	X	-
Body Surface Area (BSA) Calculation[d]	X	X	-	-	-	-
Concomitant Medication/Procedures[e]	X	X	-	X	X	X
Hematology and Serum Chemistry[f]	X	X	-	X	X	-
Adverse Event Evaluation	X	X	-	X	X	-
nab-paclitaxel Administration	X	X	-	-		-
Survival Phone Call (or chart review for documentation of last contact)	-	-	-	-	-	X
Healthcare Resource Utilization Questionnaire	X	-	-	X	X	-
Physical Examination[g]	-	-	-	X	-	-
Vital Signs[g]	X	-	-	X	-	-
Subject and Physician-Reported ECOG PS	X	-	-	X	-	-
LCSS and EQ5D-5L Questionnaires	X	-	-	X	-	-
Spirometry and Pulse Oximetry[h]	X	-	-	X	X	-
Calculated Creatinine Clearance	X	-	-	-	X	-

ALT: alanine transaminase, ANC: absolute neutrophil count, AST: aspartate transaminase, CT: computed tomography, ECOG: Eastern Cooperative Oncology Group, eCRF: electronic case report form, EQ5D-5L: EuroQol-5D, ICF: Informed Consent Form, LCSS: Lung Cancer Symptom Score, PS: performance status, WBC: white blood cell

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

[a] Scans will be performed after the completion of every 2 cycles and at treatment discontinuation (-3/+7 days). The method of assessment utilized at baseline will remain consistent throughout study duration. A complete chest CT scan with contrast, unless contraindicated, will be performed at each protocol required time point regardless of the location of the baseline disease. Scans will be archived as per institution standards.

[b] CT Scan of Head or Brain Magnetic Resonance Imaging (MRI) and Bone Scan (X-rays if needed) will be performed ONLY if deemed appropriate by the treating physician.

[c] Weight will be measured before drug administration and recorded on the appropriate eCRF page.

[d] BSA will be calculated at screening and recalculated if body weight changes by more than 10% since baseline, or since the previous visit when BSA was last recalculated and recorded in the subject's medical records. Body mass index will be a derived value, using the height, and weights reported.

[e] All concomitant medications and procedures associated with serious adverse events (SAEs) will be recorded on the eCRF from the time of signing the ICF through 28 days post last dose of investigational product(s). Reporting of concomitant medications and procedures associated with non-SAEs will include all cancer related procedures, analgesics, steroids, transfusions, growth factors, bisphosphonates, denosumab and antibiotics. All treatments and procedures provided as part of best supportive care (BSC) will require reporting on the eCRFs. During the Follow-up period, post study anti-cancer therapy and procedures will be collected and reported on the appropriate eCRF.

[f] Local laboratory assessments will be done prior to each *nab*-paclitaxel treatment during the study and as clinically indicated. ANC, WBC, platelet count, AST/serum glutamic oxaloacetic transaminase, ALT/serum glutamic pyruvic transaminase, albumin, serum creatinine, total bilirubin, prothrombin time, partial thromoplastin time and hemoglobin (Hgb) results will be collected routinely on the appropriate eCRF pages. All other routine laboratory test data will not be collected in the eCRF unless it is clinically significant, which will then be reported as an AE, and the specific associated laboratory parameter(s) will be recorded on the laboratory assessments eCRF.

[g] Physical exam and vital signs data will not be captured in the eCRFs unless deemed clinically significant by the treating physician, in which case the event will be captured as an adverse event

[h] Spirometry will be measured using an FDA approved, portable spirometer. The following values will be measured and reported on the appropriate eCRF page: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF). In addition pulse oximetry will be used to measure the saturation of peripheral oxygen (sPO_2). These data will be reported on the appropriate eCRF page. In addition the use of bronchodilators pre and post spirometry assessment will be collected on the appropriate eCRF page.

[i] All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up or death, will enter the Follow-up period. It will consist of one visit 28 days after the last dose of investigational product(s). Thereafter subjects will return to the clinic for objective scanning per the institution's policy and collection of post study anti-cancer therapy. In addition, at minimum, subjects will be contacted by phone for survival status, approximately every 90 days (+/- 14 days). Survival status can also be gleaned from clinic visits / records. All data will be reported on the appropriate eCRF for up to 1 year after the last subject is enrolled.

CELGENE PROPRIETARY INFORMATION

6. PROCEDURES

Subjects will be provided with a written informed consent form (ICF), given the opportunity to ask any questions concerning the study, and will sign an ICF prior to participating in any study procedures. After giving written informed consent, subjects will undergo a screening period to be assessed for eligibility. Subjects who do not meet the inclusion/exclusion criteria will be considered screening failures and will not be eligible for the study. Subjects that have satisfied all eligibility criteria after the screening period will be eligible for enrollment. Subjects who screen fail may re-screen 2 additional times, the ICF process will need to be performed each time, as well as all screening procedures will be repeated, unless they are still within 28 days of Cycle 1 Day 1. Assessments performed as standard of care and prior to signing the ICF for this trial, may be used to assess eligibility if performed within 28 days of Cycle 1 Day 1.

6.1. Medical History

A complete medical history including, but not limited to, evaluation for past or present significant cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatological, psychiatric, genitourinary, obstetrical, surgical history or any other diseases or disorders will be recorded at screening. The medical history will include a full review of the subject's smoking history, past and present including exposure to second hand smoke. These data will be collected on the appropriate eCRF page and will include significant past medical history up to 5 years prior to signing the ICF.

6.2. Prior Medications/Procedures

Only significant prior medications and procedures provided and or performed within 28 days of signing the ICF. All NSCLC-related prior medications, procedures, including radiation therapy, will be recorded regardless of time.

6.3. Pregnancy Testing

Serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in females of childbearing potential (FCBP) at screening. The subject may not receive treatment until the Investigator has verified that the result of the pregnancy test is negative. See inclusion criteria for pregnancy testing requirements. Any pregnancies that occur in women who have received investigational product must be immediately reported to Celgene Drug Safety, see Section 11.4.

6.4. Complete Chest Computed Tomography (CT) Scan (including adrenal gland) With and Without Contrast

A CT scan of complete chest (including the base of neck and adrenal glands) with and without contrast, unless medically contraindicated, and any other studies required for complete tumor imaging, will be done at screening, after every 2 cycles of investigational product treatment (-3/+7 days) until treatment discontinuation, lost to follow-up, withdrawal of consent or death. The same modality used at screening should be used throughout the trial. All CT scans and reports should be archived at the site according to the institution's policy. Copies will be provided to the sponsor if requested. Screening scans must be within 28 days of Cycle 1 Day 1.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

6.5. Height and Weight

Weight will be measured at screening and every treatment visit, prior to drug administration and recorded on the appropriate eCRF page. Additional weights may be measured at any time as clinically indicated. Height is only measured at baseline and will be recorded on the appropriate eCRF page.

6.6. Body Surface Area (BSA) Calculation

BSA may be recalculated if body weight changes by more than 10% since baseline or since the previous visit when BSA was last recalculated. These data will be recorded in the subject's medical record only.

6.7. Physician-Reported ECOG Performance Score

ECOG PS will be assessed and reported on the appropriate eCRF at screening, Day 1 of each cycle and at treatment discontinuation. Additional ECOG PS may be assessed and reported at any time during the study if deemed clinically necessary.

6.8. Concomitant Medications/Procedures

All concomitant medications and procedures associated with serious adverse events (SAEs) will be recorded on the eCRF from the time of signing the ICF through 28-days post last dose of investigational product(s). Reporting of concomitant medications and procedures associated with non-SAEs will include all cancer-related procedures, analgesics, steroids, transfusions, growth factors, bisphosphonates, denosumab and antibiotics. All treatments and procedures provided as part of best supportive care (BSC) will require reporting on the eCRFs. During the follow-up period, post-study anti-cancer therapy and procedures will be collected and reported on the appropriate eCRF.

6.9. Adverse Event Reporting

All subjects will have AEs recorded from the time of signing the ICF through 28 days post last dose of investigational product. See Section 11 for details.

6.10. Lung Cancer Symptom Scale, Subject- and Physician-Reported KPS, Subject-Reported ECOG PS, EQ-5D-5L, and Charlson Co-Morbidity Index

The Charlson Co-Morbidity Index will be used to measure co-existing medical conditions (other than NSCLC) at screening, for subjects in the trial. The subject-reported and physician-reported ECOG PS and KPS will be used to measure the performance status of subjects. LCSS and EQ-5D-5L questionnaires will be used to measure quality of life (QoL) for subjects in the trial. The LCSS is a 9 question survey the subject completes using a visual analogue scale (VAS) to denote intensity of a symptom. The EQ-5D comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a VAS for overall QoL. The subject-reported ECOG PS , LCSS and EQ-5D-5L questionnaires will be completed at Day 1 of every cycle, and at treatment discontinuation. The subject and physician-reported KPS will be completed on Day 1 of Cycle 1 only.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

6.11. Healthcare Resource Utilization Questionnaire

A healthcare resource utilization eCRF will be used to capture the additional use of healthcare resources, including hospitalizations, emergency room visits, doctor or nurse visits, procedures, and/or additional medication during the study period. The assessment will be completed at Day 1 of every cycle, 28-day follow-up visit and treatment discontinuation.

6.12. Electrocardiogram

An electrocardiogram (ECG) will be done at screening and as clinically indicated. However results will not be routinely collected in the eCRFs. If the results are abnormal and clinically significant at screening, the result will be recorded as medical history, and if results are abnormal and clinically significant after screening, they will be recorded as AE or SAE.

6.13. CT Scan of Head or Brain Magnetic Resonance Imaging (MRI)

CT scan of head or brain MRI will be done as clinically indicated. However the results will not be collected in the eCRFs unless deemed medically significant by the treating physician. In addition if scans show new disease involvement by NSCLC or progression of NSCLC disease, this information will be collected on the appropriate eCRF.

6.14. Bone Scans and X-rays

Bone scans and x-rays will be done as per standard of care during the study and as clinically indicated. However, the results will not be collected in the eCRFs unless deemed medically significant by the treating physician. In addition if scans show new disease involvement by NSCLC or progression of NSCLC, this information will be collected on the appropriate eCRF pages.

6.15. Physical Examinations

Physical examinations will be performed per institutional policy, at screening and treatment discontinuation, in addition to any other time as clinically indicated. However results will not be routinely collected on the eCRFs. If the findings are abnormal and clinically significant at screening, they will be recorded as medical history, and if findings are abnormal and clinically significant after screening, they will be recorded as an AE.

6.16. Vital Signs

Vital signs will be measured at screening, treatment discontinuation and any other time as clinically indicated / standard of care for the institution. However results will not be routinely collected on the eCRFs. If the findings are abnormal and clinically significant at screening, they will be recorded as medical history, and if findings are abnormal and clinically significant any time after screening, they will be recorded as an AE.

6.17. Laboratory Assessments

Local laboratory assessments will be performed at screening, prior to administration of investigational product treatment, treatment discontinuation, 28 days post last dose of investigational product and as clinically indicated. Absolute neutrophil count, white blood cell

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

count, platelet count, serum creatinine, calculated creatinine clearance, 24 hour urine collection (where applicable) hemoglobin, aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase, alanine transaminase (ALT)/serum glutamic pyruvic transaminase, albumin, total bilirubin will be recorded during the time points outlined above and captured on the appropriate eCRF page, along with the local lab normal ranges. All other laboratory values, except those mentioned above, will not be routinely reported on the eCRF.

If any laboratory value is found to be abnormal during screening, the value(s) will be recorded on the medical history eCRF with the associated NCI CTCAE grade. If any laboratory value is found to be abnormal and clinically significant post-screening, the value(s) will be recorded on the laboratory assessment eCRF along with the local lab normal range and the appropriate diagnosis will be recorded on the AE eCRF page. It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the reference ranges of the individual local laboratory. Any abnormal values that persist should be followed at the discretion of the Investigator. The Investigator should file all laboratory reports, including faxes, in the subject's medical chart.

6.18. Follow-Up / Survival

All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up or death, will enter the follow-up period. It will consist of one visit 28 days after the last dose of investigational product. Thereafter subjects will return to the clinic for objective scanning per the institution's policy and collection of post study anti-cancer therapy and procedures. In addition, at minimum, subjects will be contacted by phone approximately every 90 days (+/- 14 days) up to 1 year after the last subject is enrolled. Survival status can also be gleaned from clinic visits / records. All data will be reported on the appropriate eCRF page.

6.19. Histology and Mutation Status:

Histology will be obtained from the local pathology report and recorded on the appropriate eCRF page. Mutation status will be obtained from the local pathology report if available, these data will be collected on the appropriate eCRF page. Re-biopsies for the purpose of the study are not required.

6.20. Spirometry and Pulse Oximetry

Spirometry, per the American Thoracic Society (ATS) guidelines, will be measured using an FDA approved portable spirometer. The following values will be measured and reported on the appropriate eCRF page: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF). In addition pulse oximetry will be used to measure the saturation of peripheral oxygen (sPO_2) and these data will be reported on the appropriate eCRF page. Spirometry and pulse oximetry measurements will be performed at screening, prior to administration of investigational product on Day 1 of every cycle, investigational product discontinuation, 28 days post last dose of investigational product. In addition, those subjects prescribed bronchodilators will require spirometry assessments both pre and post bronchodilator usage. These data will be collected on the appropriate eCRF page.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

6.21. Baseline Tumor, Node and Metastasis (TNM) Stage

The baseline TNM staging will be assessed and reported by the Investigator and collected on the appropriate eCRF page.

6.22. Assessment of Nutritional Status

Nutritional status will be assessed using laboratory values, body mass index and the percentage of unintentional weight loss. Laboratory values will be analyzed and reported on the appropriate eCRFs according to Table 2 and Table 3. Body mass index will be derived using the height and weight reported on the eCRFs and the percentage of unintentional weight loss will be derived using the baseline body weight and the subject's weight approximately 6 months prior to baseline. These data will be analyzed per the description in the SAP.

6.23. Reversibility of PS 2 Status

This assessment will be made at baseline only and reported on the appropriate eCRF page.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Adults ≥ 18 years old with locally advanced or metastatic NSCLC and PS 2 who have not received chemotherapy for their advanced disease and are not candidates for curative surgery or radiation therapy, will be eligible for this study. The induction part of the study will enroll approximately 50 subjects. Subjects, after 4 cycles of *nab*-paclitaxel and carboplatin may begin monotherapy with *nab*-paclitaxel in the absence of clinical or radiological disease progression. The study will be conducted at approximately 8 to 10 sites in the United States.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled:

General and Demographics

1. Age ≥ 18 years of age at the time of signing the ICF.
2. Understand and voluntarily provide written consent to the ICF prior to conducting any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements.

Disease Specific

4. Histologically or cytologically confirmed Stage IIIB or IV NSCLC.
5. Radiographically documented measurable disease at study entry per RECIST v1.1.
6. No prior anti-cancer therapy for the treatment of metastatic disease at the time of signing the ICF. Adjuvant treatment is permitted providing cytotoxic chemotherapy was completed 12 months prior to signing the ICF and without disease recurrence.
7. Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3.
8. Platelets ≥ 100,000 cells/mm^3.
9. Hemoglobin (Hgb) ≥ 9 g/dL.
10. Aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × upper limit of normal range (ULN) or ≤ 5.0 × ULN if liver metastases.
11. Total bilirubin ≤ 1.5 × ULN except in cases of Gilbert's disease and liver metastases.
12. Serum creatinine ≤ 1.5 x ULN, or calculated creatinine clearance ≥ 40 mL/min (if renal impairment is suspected 24-hour urine collection for measurement is required).
13. Eastern Cooperative Oncology Group Performance Status 2.
14. Females of childbearing potential [defined as a sexually mature woman who (1) have not undergone hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or (2) have not been naturally postmenopausal for

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)] must:

a. Have a negative pregnancy test (ß-hCG) as verified by the study doctor within 72 hours prior to starting study therapy.

b. You must commit to complete abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study without interruption; while receiving study medication or for a longer period if required by local regulations.

Male subjects must:

c. practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 6 months following investigational product discontinuation, even if he has undergone a successful vasectomy.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Evidence of active brain metastases, including leptomeningeal involvement (prior evidence of brain metastasis are permitted only if treated and stable and off therapy for at least 21 days prior to signing ICF). MRI of the brain (or CT scan w/contrast) is preferred for diagnosis.
2. History of leptomeningeal disease.
3. Only evidence of disease is non-measurable.
4. Pre-existing peripheral neuropathy of Grade 2, 3, or 4 (per CTCAE v4.0).
5. Subject has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting investigational product (IP), and/or from whom ≥ 30% of the bone marrow was irradiated. Prior radiation therapy to a target lesion is permitted only if there has been clear progression of the lesion since radiation was completed.
6. Venous thromboembolism within 1 month prior to signing ICF.
7. Current congestive heart failure (New York Heart Association Class II-IV).
8. History of the following within 6 months prior to first administration of investigational product: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or clinically significant ECG abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder.
9. Subject has a known infection with hepatitis B or C, or history of human immunodeficiency virus (HIV) infection, or subject receiving immunosuppressive or myelosuppressive medications that would in the opinion of the Investigator, increase the risk of serious neutropenic complications.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

10. Subject has an active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
11. History of interstitial lung disease, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis.
12. Treatment with any investigational product within 28 days prior to signing the ICF.
13. History of or suspected allergy to *nab*-paclitaxel, carboplatin and human albumin or any other platinum-based therapy.
14. Currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices.
15. Any other clinically significant medical condition, psychiatric illness, and/or organ dysfunction that will interfere with the administration of the therapy according to this protocol or which, in the views of Investigator, preclude combination chemotherapy.
16. Subject has any other malignancy within 5 years prior to signing the ICF. Exceptions include the following: squamous cell carcinoma of the skin, *in-situ* carcinoma of the cervix, uteri, non-melanomatous skin cancer, carcinoma *in situ* of the breast, or incidental histological finding of prostate cancer (TNM stage of T1a or T1b). All treatment should have been completed 6 months prior to signing ICF.
17. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
18. Any medical condition that confounds the ability to interpret data from the study. This includes subjects with known psychiatric disorders.
19. Pregnant or breast-feeding females.
20. Subjects with an ECOG PS other than 2.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

8. DESCRIPTION OF INVESTIGATIONAL PRODUCT

8.1. Description of Investigational Product

Induction

Subjects will receive open-label *nab*-paclitaxel and carboplatin during the induction part of the study.

nab-Paclitaxel is designated as investigational product and will be supplied by Celgene.

Carboplatin will be supplied commercially, by prescription only.

The preparation for IV administration procedures should be followed as per the locally approved prescribing information.

Monotherapy

Subjects will receive open-label *nab*-paclitaxel.

nab-Paclitaxel is designated as investigational product and will be supplied by Celgene.

The preparation for IV administration procedures should be followed as per the locally approved prescribing information.

8.1.1. *nab*-Paclitaxel

nab-Paclitaxel is designated as investigational product and will be supplied by the Sponsor, Celgene Corporation. n*ab*-Paclitaxel is supplied in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Please see local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions and IV administration of *nab*-paclitaxel.

Temperature records for *nab*-paclitaxel must be made available to Celgene or other Sponsor-nominated monitoring teams for verification of proper investigational product storage.

8.1.2. Carboplatin

Carboplatin will be provided commercially, by prescription only.

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum diammine [1,1-cyclobutanedicarboxylato (2-)0,0']-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formula of $C_6H_{l2}N_20_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

For additional information about carboplatin storage, preparation, and administration please refer to the locally approved prescribing information.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

8.2. Treatment Administration and Schedule

Induction

Approximately 50 subjects will be treated with *nab*-paclitaxel plus carboplatin for 4 cycles.

Induction treatment will consist of:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle.
- Carboplatin AUC = 5 mg*min/mL IV on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel infusion.

Monotherapy

Subjects may begin monotherapy with *nab*-paclitaxel in the absence of clinical or radiological disease progression:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle.

8.3. Dose Delay and Dose Modifications

A dose delay will be considered if for

Day 1: Treatment to be administered is delayed, the 21-day cycle will not be considered to start until the day the investigational product is actually administered to the patient

Day 8: Treatment is $\geq$ 3 days late

- In subjects who experience any of the adverse drug reactions in Table 4 *nab*-paclitaxel on Day 1 of a cycle will not be administered until ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- In subjects who develop severe neutropenia or thrombocytopenia treatment will be withheld until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Day 8 of the cycle. Upon resumption of dosing, doses of *nab*-paclitaxel and carboplatin will be permanently reduced as outlined in Table 4. Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy. Reduced doses of *nab*-paclitaxel and carboplatin will be resumed (Table 4) when peripheral neuropathy improves to Grade 1 or completely resolves.

  For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, treatment will be interrupted until the toxicity improves to $\leq$ Grade 1, then restarted according to the guidelines in Table 4. For any other Grade 3 or 4 non-hematologic toxicity, treatment will be interrupted until the toxicity improves to $\leq$ Grade 2, then restarted according to the guidelines in Table 4.

Re-escalation is not permitted at any time.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Table 4: Permanent Dose Reductions for Hematologic and Non-Hematologic Toxicities on the Study

Adverse Drug Reaction	Occurrence	*nab*-Paclitaxel Dose (mg/m^2)	Carboplatin Dose (AUC=5 mg*min/mL)
Neutropenic Fever (ANC < 500/mm^3 with fever > 38°C) OR Delay of next cycle by > 7 days for ANC < 1500/mm^3 OR ANC < 500/mm^3 for > 7 days	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment*	
Platelet count < 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment*	
Peripheral Neuropathy Grade 3 or 4	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment*	
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis Any other Grade 3 or 4 nonhematologic toxicity	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment*	
Grade 4 cutaneous toxicity, diarrhea or mucositis	First	Discontinue Treatment*	

ANC = absolute neutrophil count; AUC = area under the curve.
* If an adverse event that requires dose reduction recurs after the dose has been reduced according to the table above, the subject should have treatment discontinued unless, at the discretion of the Investigator, there is evidence of continuing benefit to the subject that outweighs the risk of recurrent toxicity.

8.4. Method of Treatment Assignment

This is a single arm, open-label trial.

8.5. Packaging and Labeling

The label(s) for investigational product will include sponsor name, address and telephone number, the protocol number, investigational product name, dosage form and strength (where applicable), amount of investigational product per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

8.6. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

Celgene will instruct the Investigator on the return, disposal and/or destruction of investigational product and/or medical device materials if applicable. Only completely unused investigational product vials should be retained by the site until a representative from Celgene or other Celgene-designated personnel have completed an inventory. Partially used and completely used vials should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Product Accountability Record Form.

The Investigator, or designee, shall record the dispensing of investigational product to subjects in an investigational product accountability record. The investigational product record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel for the purpose of accounting for the investigational product supply. Inspections of the investigational product supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or their designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the Investigator to another Investigator or site. Under certain circumstances, and with sponsor permission, cooperative groups may manage investigational product between locations within their network as clinical trial agreement and local guidelines permit.

8.7. Investigational Product Compliance

All investigational product will be administered only by study site personnel and accurate recording of all investigational product administration will be made in the appropriate section of the subject's eCRF and source documents

8.8. Overdose

Overdose, as defined for this protocol, refers to *nab*-paclitaxel and carboplatin dosing only.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of *nab*-paclitaxel or carboplatin to a given subject, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11 for the reporting of adverse events associated with overdose.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

All supportive care is permitted in accordance with local standard of care. Subjects may receive BSC as needed per Investigator discretion and should be recorded on the appropriate eCRF pages.

BSC is defined as the best palliative care per Investigator (including but not limited to: antibiotics, analgesics, anti-emetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and/or focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis), excluding anti-neoplastic agents.

9.2. Prohibited Concomitant Medications and Procedures

Other anti-neoplastic agents or investigational products other than what is specified in the protocol are prohibited.

9.3. Required Concomitant Medications and Procedures

Not Applicable.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

10. STATISTICAL ANALYSES

Statistical analyses for the primary and key secondary endpoints of the study are described below. Additional analyses of these endpoints as well as exploratory endpoints or subgroup analyses will be described in detail in the SAP. The SAP supersedes the analyses described in the protocol should there be differences between the two.

10.1. Overview

Approximately 50 subjects will be enrolled and treated in this study. All subjects enrolled will have an ECOG performance status 2. All subjects will receive *nab*-paclitaxel 100 mg/m^2 on Days 1 and 8, and carboplatin AUC = 5 mg*min/mL on Day 1 of each 21-day cycle for the first 4 cycles. Subjects will have CT scans after every 2 cycles of investigational product treatment (-3/+7 days). At the end of 4 cycles subjects may begin monotherapy with *nab*-paclitaxel 100 mg/m^2 on Days 1 and 8 of each 21-day cycle in the absence of clinical or radiological disease progression, until documented radiologic progression or unacceptable toxicity.

Enrollment will be conducted and tracked centrally using an Interactive Response Technology (IRT) system to ensure that approximately 50% of the study population will be subjects with adenocarcinoma and 50% with squamous cell NSCLC.

The date of enrollment is defined as the date on which the subject is registered into the IRT system.

10.2. Study Population Definitions

10.2.1. Treated Population

The treated population will consist of all subjects who received at least one dose of investigational product.

10.2.2. Per-protocol (PP) Population

The PP population is defined as all eligible subjects enrolled who receive at least one dose of the investigational product and have a baseline and at least one post-baseline efficacy measurement for the endpoint of interest. Additional analyses utilizing the PP population will be described in the SAP.

10.3. Sample Size and Power Considerations

The primary objective of this study is to assess the safety and tolerability of *nab*-paclitaxel in combination with carboplatin for 4 cycles for the first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG performance status 2. All evaluations of the safety and efficacy endpoints will be based on the point estimates and the associated two-sided 95% confidence intervals rather than formal inferential statistical tests.

The primary study endpoint (also the primary safety endpoint) is the percentage of subjects who discontinue during the induction part due to TEAEs. With a sample size of 50, the maximum

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

width of the 95% confidence interval for any proportion is 28.9%. Of note, assuming the underlying percentage of subjects who will discontinue from study treatment due to TEAEs is 30%, a sample size of 50 provides 80% power, with a one-sided significance level of 10%, to detect an increase of 15 percentage points from 30%.

Table 5 below demonstrates the precision of the estimate that can be attained given a sample size of 50 for a range of hypothetical rate of study treatment discontinuation due to TEAEs during the induction part of the study. For example, for a hypothetical discontinuation rate of 30%, the width of the associated two-sided 95% confidence interval is 26.7%, and the estimated 95% confidence interval is (17.9% - 44.6%).

Table 5: Precision of the Estimate for the Treatment Discontinuation Rate due to Treatment-Emergent Adverse Events Given a Sample Size of 50

Hypothetical Discontinuation Rate due to Treatment-Emergent Adverse Events	Actual Width[a] of 95% Confidence Interval	Two-sided 95% Confidence Interval[a]
30.0%	26.7%	(17.9% - 44.6%)
35.0%	27.7%	(22.1% - 49.8%)
40.0%	28.4%	(26.4% - 54.8%)
45.0%	28.8%	(30.9% - 59.7%)
50.0%	28.9%	(35.5% - 64.5%)

[a] Estimated using the Clopper-Pearson exact method.

The analysis of both the safety and efficacy endpoints for the clinical study report will be performed at approximately 6 months after the last subject is enrolled. Subjects will be followed for OS until 12 months after the last subject is enrolled.

10.4. Background and Demographic Characteristics

The baseline characteristics of all enrolled subjects will be summarized. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Selected medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up periods. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

10.6. Safety Analysis

The treated population, which includes all enrolled subjects who received at least one dose of investigational product, will be the analysis population for all safety analyses.

The safety and tolerability of the treatment regimen will be monitored through continuous reporting and evaluated by the primary safety endpoint, TEAEs, and serious adverse events (SAEs), and incidence of subjects experiencing dose modifications, dose delay, dose interruptions during infusion, and/or premature discontinuation of investigational product.

10.6.1. Primary Safety Endpoint

The primary endpoint for this study (also the primary safety endpoint) is the percentage of subjects who discontinue study treatment during the induction part due to TEAEs.

Treatment-emergent AEs are defined as any AE or SAE occurring or worsening on or after the day of the first dose of the investigational product through 28 days after the last dose of investigational product. In addition, any serious AE with an onset date more than 28 days after the last dose of investigational product that is assessed by the Investigator as related to investigational product will be considered a TEAE.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded based on NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

10.6.2. Adverse Events

In addition to the analysis described above for the primary safety endpoint which focuses on the safety and tolerability of the induction regimen, the safety and tolerability of the treatment regimen for the entire study will be assessed by TEAE rate, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, dose delay, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death for the entire study will be summarized by MedDRA system organ class and preferred terms.

Adverse events of special interest of the *nab*-paclitaxel plus carboplatin combination identified in previous studies in a similar population may be identified and summarized by worst NCI CTCAE grade, System Organ Class (SOC) and MedDRA preferred terms.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

10.6.3. Laboratory Assessments

Hematology Parameters: In order to investigate the maximal degree of myelosuppression, the NCI CTCAE v 4.0 grades for ANC, platelet count, white blood cell (WBC) count, and hemoglobin concentration will be summarized by the most severe grade in each treatment cycle and by the most severe grade anytime during the study.

Hepatic and renal function will be summarized using the most severe NCI CTCAE grade for ALT (SGPT), AST (SGOT), total bilirubin, and creatinine clearance by cycle and at any time during the treatment.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Other laboratory parameters reported by the Investigators will also be graded by NCI CTCAE V4.0 criteria, as appropriate. All laboratory parameters will be summarized by descriptive statistics by visit.

10.6.4. Investigational Product Exposure

The extent of exposure to the investigational products will be assessed based on the descriptive statistics on the number of cycles and investigational products doses administered, cumulative dose, average dose intensity, and percentage of protocol dose administered. The incidences of *nab*-paclitaxel and/or carboplatin dose reductions, dose interruptions, and dose delays will be summarized.

10.7. Efficacy Analysis

The treated population will be the primary analysis population for all efficacy endpoints.

10.7.1. Efficacy Endpoints

10.7.1.1. Progression-free Survival

Progression-free survival is defined as the time from the date of the first dose of investigational product to the date of disease progression or death (any cause) on or prior to the data cutoff date for analyses, whichever occurred first, based on the Investigator's assessment of the data from CT scans using RECIST 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of investigational product.

Subjects who do not have disease progression and are alive as of the data cutoff date for the statistical analysis will be censored at the date of the last radiologic assessment prior to the data cutoff date. Similarly, subjects who discontinue from the study prior to disease progression or death will be censored at the date of the last radiologic assessment prior to the data cutoff date. In the event that a new anticancer treatment occurs prior to documented progression, the subject will be censored at the date of the last radiologic assessment where the subject was documented to be progression-free prior to the new anticancer treatment. Subjects with a single missing radiologic assessment prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the date of the radiologic assessment that shows progression or death (whichever is earlier). Subjects with two or more missing radiologic assessments prior to a visit with documented disease progression (or death) will be censored at the date of the last radiologic assessment where the subject was documented to be progression-free prior to the first of the two missing visits. Subjects who drop out early or die without any post-baseline radiologic tumor assessment will be censored on the date of enrollment.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time and PFS rates at 2-month intervals from the day of the first dose of IP (including two-sided 95% CI). The Kaplan-Meier curve for PFS will be presented graphically.

To assess the impact on PFS of radiologic assessments not occurring at the regularly scheduled assessment times, the frequency of these unscheduled/off-scheduled assessments will be presented.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

10.7.1.2. Disease Control Rate

Disease control rate is defined as the percent of subjects who have stable disease, complete response or partial response during the course of the study, according to RECIST 1.1 guidelines, as evaluated by the Investigator.

Disease control rate will be summarized by the observed DCR rate and the associated two-sided 95% CI.

10.7.1.3. Overall Survival

Overall survival is defined as the time between the date of the first dose of investigational product and death. All deaths, regardless of the cause of death, will be included. All subjects who are lost to follow-up prior to the end of the study or who are withdrawn from the study will be censored at the time of last contact. Subjects who are still alive as of the data cutoff date will be censored at the cutoff date. Overall survival will be summarized similarly as PFS.

10.7.1.4. Overall Response Rate

Overall response rate is defined as the percent of subjects who have a radiologic complete or partial response during the course of the study evaluated by the Investigator, according to RECIST v1.1 guidelines.

Overall response rate will be presented with the two-sided 95% CI.

10.7.2. Exploratory Endpoints

10.7.2.1. Health Care Utilization

Healthcare utilization will be summarized with all subjects treated. Additional analyses will be described in detail in the SAP.

10.7.2.2. Quality of Life and Lung Cancer Symptom Questionnaires

The score and the corresponding change from baseline at each time point will be summarized for the LCSS and EQ5D-5L. Additional analyses will be described in detail in the SAP.

10.7.2.3. Physician- and Subject-Reported ECOG Performance Status

ECOG PS scores as reported by the physician and the subject will be summarized by the actual score and change from baseline score over time. The correlation between the two sets of ECOG PS scores will be explored by cross-tabulation of the two endpoints. Other methods for exploration will be described in the SAP.

10.7.2.4. Physician- and Subject-Reported Karnofsky Performance Status

KPS as reported by the physician and the subject at baseline will be summarized. The correlation between the two sets of KPS scores will be explored by cross-tabulation of the two endpoints.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

10.7.2.5. Treatment Response During the Monotherapy Part

The number and percentage of subjects who attain a greater degree of treatment response (from stable disease [SD] to CR or PR and from PR to CR) during the monotherapy part compared with the response at the start of the monotherapy with *nab*-paclitaxel will be summarized.

10.8. Investigational Product Termination

Reasons for stopping investigational product will be presented in listings and summarized by frequency of occurrence and corresponding percentage of occurrence.

10.9. Deaths

Deaths reported during treatment (defined as deaths from the first administration of the investigational product through 28 days post last dose of the investigational product) and deaths that occur during the follow-up period will be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up).

10.10. Interim Analysis

In addition to the continuous monitoring and reporting of the TEAEs and safety-related data, an interim review of the percentage of subjects discontinued due to TEAEs will be conducted when 20 subjects have either completed 4 cycles of induction therapy, or have discontinued due to reasons other than lost to follow-up prior to completing 4 cycles of induction therapy to safeguard the safety of the subjects enrolled in the study. Data will be reviewed by the Scientific Steering Committee.

10.11. Scientific Steering Committee

A Scientific Steering Committee will be established, with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. A charter will be established for regular safety data review. The Scientific Steering Committee (SSC) will have the ability to recommend termination of the study if a safety signal is discovered. Final recommendations of the SSC will reflect the judgment of the SSC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the SSC will be made by the Sponsor.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.8 for the definition of overdose.) Any sequelae of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequelae must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of an overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for *nab*-paclitaxel or carboplatin overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of investigational product and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to investigational product. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

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

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity / intensity according to the following scale:

- *Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required*
- *Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required*
- *Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible*
- *Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable*
- *Grade 5 = Death – the event results in death*

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

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

11.2.3. Causality

The Investigator must determine the relationship between the administration of investigational product and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to investigational product administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of investigational product caused the adverse event.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

'Reasonable possibility' means there is evidence to suggest a causal relationship between the investigational product and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional investigational product that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

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

11.2.5. Action Taken

The Investigator will report the action taken with investigational product as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of investigational product, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of investigational product dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on investigational product, or within 28 days after the subject's last dose of investigational product, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the investigational product should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject receiving study medication or within 6 months after the last becomes pregnant, the male subject taking investigational product should notify the Investigator. The pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to investigational product) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of investigational product) or any SAE made known to the Investigator at anytime thereafter that are suspected of being related to investigational product. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to Celgene investigational product based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of investigational product in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

12. DISCONTINUATIONS

12.1. Treatment Discontinuation

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse event
- Disease progression
- Withdrawal by subject or treating physician
- Death
- Lost to follow-up
- Protocol violation

The reason for treatment discontinuation should be recorded in the CRF and in the source documents.

All subjects discontinued from *nab*-paclitaxel for any reason will have a treatment discontinuation visit at the time of *nab*-paclitaxel discontinuation and should undergo early termination procedures.

All subjects discontinued from *nab*-paclitaxel will return to the clinic 28 days after the last dose of investigational product for the collection of AEs.

The Investigator must notify the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE (any unacceptable toxicity). All subjects who are withdrawn from the study should complete all protocol-required evaluations scheduled for early termination at the time of withdrawal.

The reason for treatment discontinuation should be recorded in the eCRF and in the source documents.

12.2. Study Discontinuation

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The following **are** considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal of consent (decision from the subject not to provide follow-up information)

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

- Death
- Lost to follow-up

The following **may be** considered a sufficient reason for discontinuing a subject from the study:

- Protocol violation

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research Organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Product

This is an open-label study; therefore, IP will be identified on the package labeling.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, investigational products, as well as study-related duties and functions. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study-related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc...).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- Investigational product accountability records;
- Record of any body fluids or tissue samples retained;

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

CELGENE PROPRIETARY INFORMATION

EDMS Doc. Number:

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19. APPENDICES

Appendix A: ECOG Performance Status Score

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

Oken, 1982.

Appendix B: Reversible Versus Non-Reversible

If you treated this subject with doublet chemotherapy, based on your best clinical judgment do you think that you will see an improvement in their poor performance status?

This explores the concept of a patient whose poor performance status may be caused predominantly by tumor burden and may derive benefit from chemotherapy doublets to a greater degree (reversible) than a patient whose poor performance status may be caused predominantly by co-morbidities and who may not derive much benefit from chemotherapy doublets (irreversible).

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