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ABI-007-NSCL-006

A PHASE 2, OPEN-LABEL, MULTICENTER STUDY TO ASSESS SAFETY AND EFFICACY OF SECOND/THIRDLINE TREATMENT WITH NAB®-PACLITAXEL (ABI-007) IN COMBINATION WITH EPIGENETIC MODIFYING THERAPY OF CC-486, OR IMMUNOTHERAPY OF DURVALUMAB (MEDI4736), OR AS MONOTHERAPY IN SUBJECTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): ABOUND.2L+

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INVESTIGATIONAL PRODUCTS:	**CC-486, *nab*-Paclitaxel (ABI-007), durvalumab (MEDI4736)**
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PROTOCOL SUMMARY

Study Title

A Phase 2, Open-label, Multicenter Study to Assess Safety and Efficacy of Second/Third-line Treatment with *nab*®-Paclitaxel[1] (ABI-007) in Combination with Epigenetic Modifying Therapy of CC-486, or Immunotherapy of Durvalumab (MEDI4736), or as Monotherapy in Subjects with Advanced Non-small Cell Lung Cancer (NSCLC): ABOUND.2L+

Indication

Second/third-line treatment of advanced NSCLC.

Objectives

Primary

- To estimate the efficacy of *nab*-paclitaxel administered intravenously (IV) on Days 8 and 15 with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days or *nab*-paclitaxel administered intravenously (IV) on Days 1 and 8 with immunotherapy of durvalumab administered IV on Day 15 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second/third-line treatment for advanced NSCLC.

Secondary

- To estimate the relative efficacy of each of the combination therapy arms to the monotherapy arm.
- To evaluate the safety and tolerability of *nab*-paclitaxel administered intravenously (IV) on Days 8 and 15 with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days, or *nab*-paclitaxel administered intravenously (IV) on Days 1 and 8 with immunotherapy of durvalumab administered IV on Day 15 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second/third-line treatment for advanced NSCLC.

Exploratory

- To assess healthcare resource utilization for the treatment arms.
- To assess the quality of life (QoL) for the treatment arms.
- To determine baseline tumor characteristics which predict response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486 or in combination with immunotherapy of durvalumab.
- To evaluate genomic correlates of response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486 or in combination with immunotherapy of durvalumab.

[1] *nab*® is a registered trademark of Celgene Corporation.

- To evaluate anti-tumor activity of *nab*-paclitaxel/durvalumab combination therapy using Investigator assessment according to immune related response criteria updated with RECIST 1.1 (irRECIST), and its association with PD-L1 expression.

Study Design

This is a Phase 2, open-label, multicenter study to assess efficacy and safety of:

- *nab*-paclitaxel in combination with epigenetic modifying therapy of CC-486,
- *nab*-paclitaxel in combination with immunotherapy of durvalumab,
- and *nab*-paclitaxel monotherapy

as second/third-line treatment in subjects with advanced NSCLC who have received no more than one prior chemotherapy regimen. Approximately 240 subjects with advanced NSCLC will be assigned 1:1:1 into one of the following treatment arms: *nab*-paclitaxel /CC-486 combination therapy, *nab*-paclitaxel /durvalumab combination therapy or *nab*-paclitaxel monotherapy prior to receiving the first dose of investigational product (IP). Randomization/treatment assignment strategy of subjects to the three treatment arms is described in the Overview of Statistical Methods below and in Section 10.1.

The study will consist of up to a 28-day Screening Period, a Treatment Period and a Follow-up Period.

The Screening Period for eligibility determination begins upon subject written informed consent. All screening assessments must be completed within 28 days prior to first dose of IP.

The Treatment Period begins with the first dose of IP as described in Section 8. Subjects will receive one of the following treatments based on the randomization/treatment assignment:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 and durvalumab 1125 mg IV infusion over approximately 1 hour on Day 15 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zoledronic acid, denosumab) is permitted as per the Investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the Sponsor. Subjects in the *nab*-paclitaxel/durvalumab arm may continue treatment beyond disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 as described in Section 4.1.2.1.

Tumor evaluations will be assessed by the investigative sites and response will be determined according to RECIST guidelines, Version 1.1 (Eisenhauer, 2009), and immune-related RECIST criteria (irRECIST) when applicable.

All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an adverse event (AE)/serious adverse event (SAE) and also recorded on the laboratory electronic Case Report Form (eCRF) (see Section 11.3).

All subjects who discontinue from treatment for any reason other than withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor will enter the Follow-up Period. It will consist of a visit 28 days after the last dose of IP or End of Treatment Visit, whichever is later. Thereafter, subjects in the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms will be followed for survival by phone call contact approximately every 90 days (+/- 14 days) for at least 12 months after the last subject is randomized/assigned in either arm or 120 progression-free survival (PFS) events have been observed between these two arms, whichever comes later. Subjects in the *nab*-paclitaxel/durvalumab arm will be followed for survival in a similar manner for at least 12 months after the last subject is assigned to this arm.

During the study, subjects will have computed tomography (CT) scans every 42 days (-3/+7 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. Subjects in the *nab*-paclitaxel/durvalumab arm who continue beyond disease progression per RECIST 1.1 will continue to have CT scans every 42 days (-3/+7) until progression per immune-related RECIST criteria (irRECIST 1.1) (Nishino, 2013). Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. All post-treatment anticancer therapies will be recorded during the Follow-up Period.

Study Population

Male and female subjects with advanced NSCLC who have received no more than one prior chemotherapy regimen for their advanced disease will be eligible for this study (immunotherapy in prior line of treatment is allowed, including platinum doublet combination). Subjects will receive study therapy as second or third line of treatment for advanced disease.

Length of Study

The enrollment of 240 subjects on this study will take approximately 28 months. The total length of this Phase 2 study with follow-up for survival is estimated to be approximately 40 months.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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 prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will receive *nab*-paclitaxel in combination with CC-486 or durvalumab, or *nab*-paclitaxel monotherapy during the study. The CC-486, *nab*-paclitaxel, and durvalumab are designated as IP and will be packaged and supplied by the Study Sponsor.

Overview of Statistical Methods

The primary objective of this study is to estimate the efficacy of the CC-486 and *nab*-paclitaxel combination therapy, that of the durvalumab and *nab*-paclitaxel combination therapy, and that of the *nab*-paclitaxel monotherapy. The secondary efficacy objective is to estimate the relative efficacy of each of the combination regimens to the monotherapy regimen and the tolerability of each of the 3 treatment regimens.

Approximately 240 subjects will be assigned to one of the three treatment arms (approximately 80 subjects per group). A permuted-block randomization method will be employed to assign the subjects among the treatment arms that are enrolling simultaneously, stratified by the following baseline factors: ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no). Randomization/treatment assignment of subjects will be carried out centrally using an Interactive Response Technology (IRT) system. Prior to Protocol Amendment 4.0, all subjects were randomized 1:1 to the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms. As Protocol Amendment 4.0 implementation was in effect after enrollment in the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms completed with each reaching approximately 80 subjects, all subjects enrolled while Protocol Amendment 4.0 is in effect and at the time of Protocol Amendment 5.0 implementation will be assigned to the *nab*-paclitaxel/durvalumab combination therapy arm until approximately 80 subjects have been enrolled in that arm. Hence, treatment assignment of subjects to the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms was in effect conducted completely in a randomized fashion and randomization between the *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms will not apply.

Evaluations of the study endpoints will be based primarily on the point estimates and the associated 95% confidence intervals of the within- and between-treatment differences (each combination therapy vs. monotherapy).

An independent Data Monitoring Committee (DMC) will be established to review the interim safety and efficacy data.

Efficacy Analyses

The intent-to-treat population, which includes all randomized (or assigned) subjects regardless of whether the subject receives any IP or has any efficacy assessments performed, will be used for all efficacy analyses. The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization/treatment assignment 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 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of study therapy.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time (including two-sided 95% confidence interval [CI]) for each treatment arm. The relative treatment effect between each of the combination therapy and monotherapy arms with respect to PFS will be estimated by the hazard ratio (HR) and the associated two-sided 95% CIs using the stratified Cox proportional hazard model with ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no) as the stratification factors. No statistical inferential tests will be performed. To explore the effect of treatment post initial progression,

PFS defined by irRECIST criteria may be estimated for those subjects in the *nab*-paclitaxel/durvalumab combination arm.

The secondary endpoints include disease control rate (DCR), overall response rate (ORR), and overall survival (OS). Disease control rate and ORR will be summarized within each treatment arm by the observed rates and the associated 95% CIs. The relative treatment effect of each of the combination therapy arms to the monotherapy arm will be summarized by the ratio of the observed rates. Overall survival will be analyzed using similar statistical methods as that for the PFS endpoint.

Safety Analyses

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

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as any AE or SAE occurring or worsening on or after the day of the first dose of the IP through 28 days after the last dose of the last IP administration.

In addition, any SAE with an onset date more than 28 days after the last dose of IP that is assessed by the Investigator as related to IP will be considered a TEAE. For the *nab*-paclitaxel/durvalumab arm, AEs with an onset from 29 days up to 90 days after the last dose of any IP will be summarized separately.

Treatment-emergent adverse events, Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose reduction, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized by treatment arms using MedDRA system organ class and preferred terms.

Sample Size

This study is designed primarily to estimate the treatment effect within each of the combination and monotherapy arms and secondarily the relative effect between each of the combination therapy and the monotherapy arms with respect to the primary and secondary efficacy endpoints. The sample size was chosen to support the estimation of the within- and between-treatment effects with reasonable precision. Table 1 below summarizes the precisions that can be achieved given different scenarios of hypothetical observed hazard ratios between the two treatment arms for PFS events, assuming a total of approximately 120 events are observed between two treatment arms, and the time to PFS has an exponential distribution.

Table 1: Progression-Free Survival – Two-sided 95% Confidence Interval of Hypothetical Observed Hazard Ratio between Treatment Arms

Hypothetical Number of Events Observed	Hypothetical Observed Hazard Ratio of PFS Events	95% Confidence Interval of Hazard Ratio[a]
120	0.60	(0.42, 0.86)
	0.65	(0.45, 0.93)
	0.70	(0.49, 1.00)

[a] Assuming a standard error of 0.18 for the log hazard ratio.

Assuming the median times of PFS are 4.17, 4.25 and 2.5 months, respectively, for the *nab*-paclitaxel/CC-486 combination therapy, the *nab*-paclitaxel/durvalumab combination therapy and *nab*-paclitaxel monotherapy arms, and an approximate 28 months accrual period for a total of approximately 240 subjects, it is estimated that an approximate total of 170 PFS events among the three arms will be observed by approximately 3 months after the last subject is assigned to the *nab*-paclitaxel/durvalumab arm, assuming an exponential distribution for PFS.

One nonbinding interim analysis for PFS with early stopping rule for futility will be conducted when approximately 60 events have been observed between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms. An additional non-binding interim analysis for futility with early stopping rule with the PFS endpoint between the *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms will be conducted when approximately 30 PFS events have been observed in the *nab*-paclitaxel/durvalumab arm (60 or more events are expected to have occurred in the monotherapy arm at that point).

At the interim analysis data review on , based on the recommendation of the DMC, treatment with CC-486 will be discontinued in the *nab*-paclitaxel/CC-486 combination arm; subjects in this arm may be allowed to continue on *nab*-paclitaxel single agent, at the Investigator's discretion.

Similarly, following the outcome of the interim analysis between *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms, and taking into account the DMC recommendations, subjects may be allowed to remain on either *nab*-paclitaxel or durvalumab as a single agent or both agents, at the Investigator's discretion.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the trial Coordinating Investigator and Steering Committee. A DMC charter will be established.

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1. INTRODUCTION

1.1. 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 (http://www.lungcancercoalition.org/en/pages/about/awareness).

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

Platinum-containing chemotherapy regimens remain (eg, platinum-based agents with taxanes) the standard first-line treatment in the US and Japan. 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 (NICE, 2011). For first-line therapy in patients with Stage IV NSCLC and good performance status, the American Society of Clinical Oncology (ASCO) clinical practice guideline recommends treatment with a platinum-based two-drug combination of cytotoxic drugs (Azzoli, 2009). For patients without disease progression, the option of maintenance monotherapy with pemetrexed or erlotinib could also be considered (Gerber, 2013; Schiller, 2013). A trend that is becoming more prevalent is personalized NSCLC treatment based on tumor histology (squamous versus nonsquamous), on molecular characteristics of the tumor, and on the patient's clinical status using agents targeting specific receptors, kinases and pathways (ie, epidermal growth factor receptor [EGFR], echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

Single agent chemotherapy (pemetrexed, EGFR-inhibitors and taxanes) are standards of care for second-line treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel has been widely evaluated in this setting, and is currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy (the US label specifies prior platinum-based chemotherapy). For patients with a good performance status at the time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, was associated with a 10% to 20% prolongation of 1-year survival and an improved quality of life when compared with ifosfamide, vinorelbine, or best supportive care (BSC) alone (Hanna, 2004). Erlotinib is indicated in the US and EU for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, although no survival benefit has been demonstrated in patients with EGFR-IHC negative tumors. Pemetrexed is indicated in the US and EU as a single agent for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC after prior chemotherapy. However, the approval and subsequent increased use of pemetrexed and erlotinib in the first-line setting poses an unmet need in the second-line setting, whereby new therapeutic options are needed.

Recently, nintedanib, a triple angiokinase inhibitor, was approved in the European Union (EU) in combination with docetaxel as second-line therapy for NSCLC. The results showed that compared to docetaxel alone, nintedanib plus docetaxel significantly extended the median OS from 10.3 to 12.6 months for patients with advanced adenocarcinoma, after first-line chemotherapy (p = 0.0359; hazard ratio [HR]: 0.83) (Reck, 2014a). In addition, ramucirumab was approved in the US in combination with docetaxel as second-line therapy. The Phase 3 REVEL trial compared ramucirumab, a vascular endothelial growth factor (VEGFR)-2 antagonist, plus docetaxel with placebo plus docetaxel in NSCLC patients who experienced disease progression after treatment with platinum-based chemotherapy for locally advanced or metastatic disease. Median OS was better in the ramucirumab group than in the placebo group (10.5 vs 9.1 months; HR, 0.857; p = .0235), as was median progression-free survival (PFS) (4.5 vs 3.0 months; HR, 0.762; p < .0001) (Garon, 2014).

More recently, advances in immunotherapy have seen approvals of nivolumab (US and EU) and pembrolizumab (US) in the advanced NSCLC setting after prior chemotherapy. In this setting, nivolumab has shown benefit in overall survival with 9.2 months (95% CI, 7.3 to 13.3) versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel in advanced squamous NSCLC (Checkmate 017 study) (Brahmer, 2015), and 12.2 months (95% CI, 9.7 to 15.0) versus 9.4 months (95% CI, 8.1 to 10.7) with docetaxel (HR 0.73; 95% CI, 0.59 to 0.89; p = 0.002) in nonsquamous disease (Checkmate 057 study) (Borghaei, 2015). However, PFS benefit was modest (3.5 months with nivolumab versus 2.8 months with docetaxel (HR 0.62; 95% CI, 0.47 to 0.81; p <0.001) or did not favor nivolumab in these populations. Regarding its safety profile, nivolumab is most commonly associated with immune-related adverse reactions. Most of these including severe reactions resolved following initiation of appropriate medical therapy, or withdrawal of nivolumab. In the pooled dataset of two studies in squamous NSCLC, the most frequent adverse reactions were fatigue (33%), decreased appetite (15%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grades 1 or 2) (Opdivo® Prescribing Information). In comparison, the efficacy of pembrolizumab was investigated in a sub-group of a cohort of 280 patients enrolled in a multicenter, open-label multi-cohort, activity-estimating study which showed an overall response rate (ORR) of 41% (95% CI, 29 to 54) in both squamous and nonsquamous subjects. Serious adverse reactions occurred in 38% of patients receiving pembrolizumab and the most frequent reported in at least 2% of patients were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis (Keytruda® Prescribing Information).

Similarly and as will be described below, the PD-L1 inhibitor durvalumab has demonstrated encouraging clinical activity both as a monotherapy and in combination with other agents including standard chemotherapies in metastatic melanoma, NSCLC and other advanced solid tumors, with acceptable and manageable reported toxicities.

1.2. *nab*-Paclitaxel in NSCLC

nab-Paclitaxel is approved in the first-line setting in combination with carboplatin for patients with NSCLC in the US, EU, Japan, Argentina, Australia, New Zealand and other countries. The approval was based on the evaluation of Phase I and II data (Belani, 2008; Rizvi, 2008; Socinski, 2010), as well as the pivotal Phase 3 study (CA031), (Socinski, 2012). The pivotal Phase 3 study was a multicenter, randomized, open-label study conducted in 1052 chemo-naïve subjects with

Stage IIIB/IV NSCLC to compare *nab*-paclitaxel in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced NSCLC. *nab*-Paclitaxel was administered as an IV 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 IV 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 IV 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 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 performance status (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%; response rate ratio, 1.313; 95% CI, 1.082 to 1.593; p = 0.005), see Table 2].

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. Overall survival in the *nab*-paclitaxel arm was 12.1 months versus 11.2 months in the control arm (p = 0.271; HR = 0.922). There was an approximately 10% increase in PFS in the *nab*-p/C versus P/C arm and PFS in the nab-p/C arm was noninferior to PFS in the P/C arm ($HR_{nab\text{-}p/C/P/C}$ 95% CI upper bound, 1.086).

Table 2: 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/P_T: 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.

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

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 versus paclitaxel injection plus carboplatin (Grades 1 to 4 [and Grade 3/4]) were: anemia (98% vs 91% [28% vs 7%]), neutropenia (85% vs 83% [47% vs 58%]) and thrombocytopenia (68% vs 55% [18% vs 9%]).

1.3. Rationale for *nab*-Paclitaxel as Second/Third-line Treatment in Subjects with Advanced NSCLC

Patients who fail first-line chemotherapy are eligible for second-line treatment with single agent docetaxel, pemetrexed or erlotinib. In patients with good performance (eg, ECOG PS 0 or 1) and general health status, further treatment with chemotherapy is an important consideration that has been shown to extend overall survival. Despite the availability of second-line therapy, the trend of increased use of pemetrexed, as well as erlotinib (in selected patients) in the first-line and maintenance settings, potentially limits the number of available second-line treatment options for many patients. Furthermore, the tolerability issues associated with the administration of docetaxel once every 3 weeks (q3w) has prompted active research in the past decade to evaluate whether weekly regimens of taxanes could be optimized to improve the toxicity profile. The availability of an effective second-line cytotoxic chemotherapy with an improved efficacy/safety profile over current available options would be a valuable addition for both the patient and the treating physician. Paclitaxel has also demonstrated potential activity in second-line NSCLC in a few studies (Socinski, 1999; Juan, 2002; Socinski, 2002; Sculier, 2002; Buccheri, 2004; Ceresoli, 2004; Yasuda, 2004). More recently, advances in immunotherapy have seen increased use of immune checkpoint inhibitors (eg, nivolumab, pembrolizumab) in the first and/or second-line setting for advanced NSCLC disease.

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, when compared with paclitaxel (Desai, 2006; Gardner, 2008). Distribution of *nab*-paclitaxel to peripheral tissues as demonstrated in a recent study was 4-fold faster and 10-fold more extensive than of Cremophor EL-paclitaxel micelles, which results in a unique and distinct profile of paclitaxel in tissues (Li, 2015). The Cremophor EL-free medium enables *nab*-paclitaxel to be given over a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions, thus also avoiding negative impact of steroids on paclitaxel induced apoptosis and decreased antitumoral activity of chemotherapeutic agents as reported in pre-clinical models glucocorticoids (Abraxane® Prescribing Information; Zavodovskaya, 2015; Herr, 2003; Sui, 2006; Khan, 2013; Pang, 2006).

When administered with carboplatin in the first-line setting, weekly *nab*-paclitaxel has demonstrated a more favorable efficacy:safety profile compared to the every 3 weeks schedule. This weekly schedule of *nab*-paclitaxel allows the opportunity for closer (ie, shorter interval) monitoring of side effects and optimizing dose-intensity through timely adjustments.

Finally, recently published data has demonstrated efficacy of *nab*-paclitaxel as monotherapy in the second line setting in advanced NSCLC with ORR ranging from 16.1% to 33% and a median PFS of up to 5 months (Chen, 2012; Saxena, 2012; Yuan, 2012).

Rationale for dose and schedule

As previously noted, *nab*-paclitaxel 100 mg/m^2 weekly (Days 1, 8 and 15) in combination with carboplatin (21 day cycle) is approved in the US, EU, Japan, Argentina, Australia, New Zealand and other countries for the treatment of locally advanced or metastatic NSCLC in the first-line setting. However, there is limited data of monotherapy *nab*-paclitaxel in the second or third-line setting; hence, this study will assess the efficacy and tolerability of weekly *nab*-paclitaxel, when administered on Days 1 and 8 of each 21-day cycle. The allowance of a one week rest period in this study (ie, no treatment on Day 15), takes into account research findings from other taxanes, whereby patients in the second-line setting are unlikely to tolerate the same dose-intensity compared to chemo-naïve patients (eg, sharper dose reduction in the second-line setting). Therefore, the proposed *nab*-paclitaxel schedule (2 weeks treatment, 1 week rest) could offer the option of maintaining consistent dose-intensity for NSCLC patients in this setting.

1.4. Rationale for *nab*-Paclitaxel in Combination With Epigenetic Modifying Therapy of CC-486 as Second/Third-line Treatment in Subjects with Advanced NSCLC

CC-486 is an orally bioavailable formulation of the nucleoside analog 5-azacitidine (AZA). After its incorporation into a cell's DNA during the S-phase of the cell cycle, CC-486 forms covalent adducts with DNA Methyltransferase 1 (DNMT1) and depletes this enzyme required for the maintenance of DNA methylation patterns, thereby altering the epigenetic status of the cell.

Epigenetic changes are covalent modifications of chromatin (DNA and histone proteins) that mediate the stable transmission of a gene's transcriptional status through cell division. One of the first recognized epigenetic alterations in cancer was DNA methylation. The addition of a methyl group to cytosine in the dinucleotide CpG is catalyzed by DNA methyltransferases (DNMTs) and is associated with transcriptional repression of genes with high density of CpGs (CpG islands) in the vicinity of their promoters (Jones, 2007). Genomic methylation patterns are precisely regulated during normal embryonic development and differentiation and have been found to be altered in specific ways in cancer. Specifically, cancer cell genomes are typified by reduced methylation globally with focal areas of aberrant hypermethylation in the CpG islands of genes encoding known tumor suppressors such as PTEN and BRCA1 as well as genes encoding proteins required for apoptosis, including caspase 8, DAPK and Apaf-1. DNA methylation-based silencing can thus contribute to the establishment and maintenance of the transformed state and limit the effectiveness of anti-cancer therapies. The recognition of the role of aberrant methylation in carcinogenesis and its reversibility has led to the development of DNMT inhibitors for cancer. Subcutaneous (SC) AZA was the first DNMT inhibitor to be approved in myelodysplastic syndromes (MDS) in 2004 (Kaminskas, 2005).

The notion that sequential treatment with an epigenetic modifying agent followed by a cytotoxic agent can result in improved response to the latter is supported by numerous preclinical experiments and now by early clinical results. In breast cancer cell lines, restoring expression of the aberrantly methylated pro-apoptotic gene TMS1 with azacitidine can restore taxane

sensitivity (Gordian, 2009). In a model of platinum resistant ovarian cancer, azacitidine reversed resistance to carboplatin (Li, 2009). This effect required pretreatment of the cells with noncytotoxic levels of azacitidine for 24 hours before the addition of carboplatin and was not observed with concurrent exposure to both agents. More recently, Juergens and colleagues observed an unusually high ORR of approximately 20% in multiple-relapsed NSCLC patients treated with a variety of regimens after being treated with a combination of SC AZA and another epigenetic agent, entinostat, a histone deacetylase inhibitor (Juergens, 2011). In one case, a patient who had previously progressed on a regimen of paclitaxel, carboplatin and bevacizumab responded to the same triplet after treatment with SC AZA and entinostat, suggesting that the epigenetic modifying agents had reversed acquired resistance to the cytotoxic/anti-angiogenic regimen. In a Phase 1/2 study of SC AZA with *nab*-paclitaxel in subjects with advanced metastatic solid tumors and breast cancer (Dumlao, 2011), escalating doses of SC AZA (75 to 100 mg/m^2) were administered on Days 1 through 5, followed by *nab*-paclitaxel (100 mg/m^2) intravenous (IV) on Days 8, 15, and 22 of a 28-day cycle. Of 16 subjects treated at the time of publication, clinical activity has included 3 complete responses (CR, 1 Diffuse Large B-cell Lymphoma [DLBCL], 2 ovarian), 4 partial responses (PR) in ovarian and endometrial cancer and 4 stable diseases (SD, 2 lung, 1 pancreatic, and 1 sarcoma).

CC-486 entered clinical testing in 2006 in subjects with MDS, chronic myelomonocytic leukemia [CMML], and acute myeloid leukemia [AML], with daily extended dosing schedules of 14 and 21 out of 28 days in a non-crossover fashion. Daily doses of 300 mg CC-486 have proven to be tolerated on both the 14 and 21 out of 28-day schedules with myelosuppression, gastrointestinal symptoms, and fatigue being the most common toxicities (Garcia-Manero, 2011). Subjects treated with CC-486 for 14 or 21 days had DNA hypomethylation that persisted through the end of cycle. This contrasts with the lack of persistent hypomethylation at the end of cycle when subjects were treated with SC AZA for 7 out of 28 days.

This Phase 2 study will test the hypothesis that epigenetic modifying therapy with CC-486 can improve the anti-tumor activity of *nab*-paclitaxel in second/third-line NSCLC patients (see Section 4.2 for study rationale). Although docetaxel has been assessed in other randomized studies as a chemotherapy backbone, the considerable neutropenia-related toxicity could potentially pose safety concerns if combined with CC-486, and the steroid premedication could confound the epigenetic impact of CC-486. In addition, the q3w dosing schedule of docetaxel restricts dose adjustment options, thus potentially yielding lower chemotherapy dose-intensity.

Please refer to the Investigator's Brochures (IBs) of CC-486 and *nab*-paclitaxel (ABI-007) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IPs.

1.5. Rationale for *nab*-Paclitaxel in Combination With Immunotherapy of Durvalumab as Second/Third-line Treatment in Subjects with Advanced NSCLC

Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 to PD-1 and CD80 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.

To date durvalumab has been given to more than 1900 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

A Phase 2 trial of durvalumab is currently ongoing to assess efficacy and safety of the immune checkpoint inhibitor (dose of 10 mg/kg once every two weeks [q2w]) in patients with locally advanced or metastatic NSCLC in the third-line setting (Rizvi, 2014) (ATLANTIC trial, NCT02087423).

Preliminary data of an open-label Phase 1b study of durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg in immunonaive patients with advanced or metastatic squamous or non-squamous NSCLC showed a manageable tolerability profile, with antitumor activity irrespective of PD-L1 status (ORR 22%, 95% CI 9-44) (Antonia, 2016).

***nab*-Paclitaxel in combination with immune checkpoint inhibitors**

Tumor lysis as a consequence of chemotherapy treatment leads to release of tumor antigens, which in turn are recognized by the immune system, thus priming the immune system for checkpoint inhibitor activity (Bracci, 2014; Chen, 2013; Mellman, 2011). Accumulating evidence suggests that immune activation plays an important role in chemotherapy efficacy (Zitvogel, 2013). In addition to increasing tumor antigenicity, chemotherapy also reduces tumor burden and acts directly on immune cell populations, activating dendritic cells, depleting immunosuppressive regulatory T cells at low doses, depleting myeloid-derived suppressor cells, and increasing tumor-infiltrating lymphocytes (Tanaka, 2009; Banissi, 2009; Kodumudi, 2010; Dieci, 2014). Taxanes have been shown to facilitate dendritic cell maturation and cytokine secretion (Chen, 2013a). In patients with lung cancer, paclitaxel was associated with generation of pro-inflammatory markers, including interleukin 2 and interferon gamma, and the expression of T cell activation markers (Zhang, 2008). Taxanes have been demonstrated to modulate the immune system by impairing regulatory T cells, which are drivers of peripheral tolerance, but not effector T cells, which are drivers of tumor-cell killing (Tanaka, 2009). Taxanes are also known to act on myeloid cells such as myeloid-derived suppressor cells and alternatively

differentiated (M2) macrophages to decrease their immunosuppressive functions (Kodumudi, 2010).

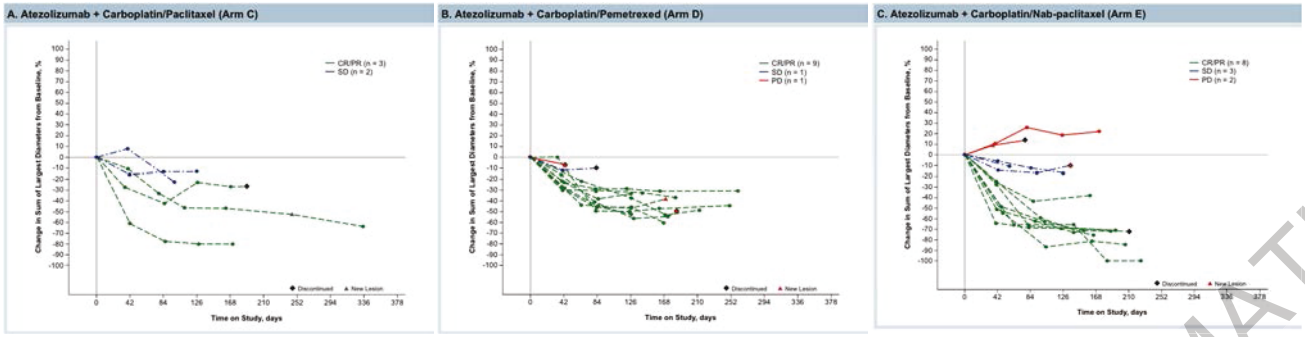
The data above suggest a potential for synergistic activity of cytotoxic therapy, such as taxanes, with checkpoint inhibitors, including those that target PD-1 or PD-L1. *nab*-Paclitaxel has demonstrated cytotoxic activity in non-small cell lung cancer (overall response rate = 33% vs 25% with paclitaxel in a Phase III trial) (Socinski, 2012) and, as stated above, does not require steroid pretreatment, which may make it a logical choice for combination with immune checkpoint inhibitor.

Therefore, this Phase 2 study will further assess the potential synergistic activity of *nab*-paclitaxel, a cytotoxic agent, in combination with the anti-PD-L1 checkpoint inhibitor durvalumab in second/third-line treatment for advanced NSCLC, from an efficacy and safety standpoint. The current study will allow patients who progress on prior checkpoint inhibitor therapy (eg, as their first-line or second-line therapy) as it is hypothesized that the companion chemotherapy of nab-paclitaxel may re-sensitize the disease to allow patient to respond to checkpoint inhibitors.

- ***nab*-Paclitaxel in combination with anti-PD-L1**

More recently, preliminary results of an ongoing Phase 1b trial in first line metastatic NSCLC of another immune checkpoint anti-PD-L1 inhibitor, atezolizumab, showed high response rates in combination with the following platinum-based doublets: 60 % (95% CI: 15-95) in the carboplatin/paclitaxel cohort (Arm C; n = 5), 75% (95% CI: 43-95) in the carboplatin/pemetrexed arm (Arm D; n=14), and 62 % (95% CI: 32-86) with four patients experiencing complete response when atezolizumab was combined with carboplatin/*nab*-paclitaxel regimen (Arm E; n=13) (Liu, 2015). The most frequent AEs included nausea (Arms C and D, 50%; Arm E, 73%), fatigue (Arm C, 38%; Arm D, 36%; Arm E, 73%) and constipation (Arm C, 25%; Arm D, 71%; Arm E, 27%). The most common MPDL3280A-related Grades 3 to 4 AEs included anemia (Arms D and E, 7%), neutropenia (Arm C, 13%; Arm D, 7%) and thrombocytopenia (Arms D and E, 7%). No pneumonitis was seen. One MPDL3280A-related Grade 5 AE due to candidemia after prolonged neutropenia was seen in Arm D. Thirty patients were efficacy evaluable (Arm C, 5; Arm D, 12; Arm E, 13). Overall, treatment with atezolizumab plus chemotherapy (including maintenance therapy) was well tolerated, without apparent exacerbation of chemotherapy-associated adverse events.

Figure 1: Anti-PD-L1 in Combination with Platinum-Based Doublets



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- ***nab*-Paclitaxel in combination with anti-PD-1**

An ongoing Celgene-sponsored Phase 1 trial (NCT02309177) in solid tumors is assessing the safety and efficacy of the anti-PD-1 agent nivolumab in combination with *nab*-paclitaxel and carboplatin in a cohort of subjects with advanced NSCLC patients in the first-line setting (*nab*-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 and carboplatin AUC 6 on Day 1 of each 21-day cycle (Cycles 1 to 4 only); nivolumab 5 mg/kg on Day 15 of each 21-day cycle starting in Cycle 1). Preliminary results show that amongst the 9 subjects having received study treatment including nivolumab, 6 had partial responses and 3 stable disease. No dose limiting toxicities were observed. Most common AEs were low grade vomiting, diarrhea, alopecia, peripheral neuropathy and neutropenia (data on file). These results are consistent with another Phase 1 trial comparing anti-PD-1 antibody nivolumab (10 mg/kg IV q3w) combined with three different platinum-doublet regimens in 52 patients with chemotherapy-naïve advanced NSCLC, with a reported ORR of 33% with gemcitabine/cisplatin, 47% with pemetrexed/cisplatin, as well as with paclitaxel/carboplatin, while stable disease was reported in 58%, 47%, and 27% of subjects, respectively (Checkmate 012; NCT01454102); (Antonia, 2014). Grades 3 to 4 treatment-related adverse events were reported in 45% of patients (25% to 73% across arms), including pneumonitis (4 patients, 7%; managed by protocol algorithm), and fatigue and acute renal failure (3 patients, 5% each).

Rationale for fixed dose and schedule

[redacted]

Similarly, a population PK model

was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg q4w or once every 90 days (Q90D); metastatic melanoma) (Wang, 2014). A population PK model indicated minor impact of body WT on the PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg q4w) and fixed dosing (75 mg/kg q4w; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using a population PK model in a simulated population of 1000 patients with body WT distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (Ng, 2006; Wang, 2009; Zhang, 2012; Narwal, 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/PD parameters (Zhang, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, it is considered feasible to switch to fixed dosing regimens.

Sequential administration of chemotherapy and checkpoint inhibitor will allow for limitation of potential interactions and better management of toxicities.

Please refer to the Investigator's Brochures (IBs) of durvalumab and *nab*-paclitaxel (ABI-007) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational products (IPs).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To estimate the efficacy of *nab*-paclitaxel administered intravenously (IV) on Days 8 and 15 with epigenetic modifying therapy of CC-486 once daily (QD) on Days 1 to 14 every 21 days, or *nab*-paclitaxel administered intravenously (IV) on Days 1 and 8 with immunotherapy of durvalumab administered IV on Day 15 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second/third-line treatment for advanced NSCLC.

2.2. Secondary Objective

The secondary objective of the study is:

- To estimate the relative efficacy of each of the combination therapy arms to the monotherapy arm.
- To evaluate the safety and tolerability of *nab*-paclitaxel administered IV on Days 8 and 15 with epigenetic modifying therapy of CC-486 QD on Days 1 to 14 every 21 days, or *nab*-paclitaxel administered intravenously (IV) on Days 1 and 8 with immunotherapy of durvalumab administered IV on Day 15 every 21 days, and *nab*-paclitaxel monotherapy administered IV on Days 1 and 8 every 21 days as second/third-line treatment for advanced NSCLC.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess healthcare resource utilization for the treatment arms.
- To assess the quality of life (QoL) for the treatment arms.
- To determine baseline tumor characteristics which predict response to *nab*-paclitaxel as a single agent and with epigenetic modifying therapy of CC-486 or immunotherapy of durvalumab.
- To evaluate genomic correlates of response to *nab*-paclitaxel as a single agent and with epigenetic modifying therapy of CC-486 or immunotherapy of durvalumab.
- To evaluate anti-tumor activity of *nab*-paclitaxel/durvalumab combination therapy using investigator assessment according to immune related response criteria updated with RECIST 1.1 (irRECIST), and its association with PD-L1 expression.

3. STUDY ENDPOINTS

Study efficacy endpoints will be assessed by the Investigator using RECIST 1.1 guidelines.

3.1. Primary Endpoint

The primary endpoint is:

- Progression free survival.

3.2. Secondary Endpoints

The secondary endpoints are:

3.2.1. Efficacy

- Disease control rate.
- Overall response rate.
- Overall survival.

3.2.2. Safety

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

3.3. Exploratory Endpoints

- Healthcare resource utilization during the study via patient feedback.
- Changes in the Lung Cancer Symptom Scale (LCSS), European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30, and EuroQoL 5D-5L (EQ-5D-5L).
- The correlation between pretreatment tumor characteristics and response to the study treatment determined using next-generation sequencing methods, immunohistochemistry, or other analysis methods.
- Analysis of PFS and DCR and their association with PD-L1 expression using Investigator's assessments according to irRECIST.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, open-label, multicenter study to assess safety and efficacy of:

- *nab*-paclitaxel in combination with epigenetic modifying therapy of CC-486,
- *nab*-paclitaxel in combination with immunotherapy of durvalumab,
- and *nab*-paclitaxel monotherapy

as second/third-line treatment in subjects with advanced NSCLC who have received no more than one prior chemotherapy regimen. Approximately 240 subjects with advanced NSCLC will be assigned 1:1:1 into one of the following treatment arms: *nab*-paclitaxel/CC-486, *nab*-paclitaxel/durvalumab combination therapy or *nab*-paclitaxel monotherapy prior to receiving the first dose of investigational product (IP). Randomization (details in Section 10.1), when conducted, will be centralized and stratified by ECOG performance status (0 versus 1, see Appendix A), gender (males versus females), and smoker (yes versus no).

The study will consist of up to a 28-day Screening Period, a Treatment Period and a Follow-up Period.

4.1.1. Screening Period

The Screening Period for eligibility determination begins upon subject written informed consent. All screening assessments must be completed within 28 days prior to first dose of IP.

4.1.2. Treatment Period

The Treatment Period begins with the first dose of IP as described in Section 8. Subjects will receive one of the following treatments based on the randomization/treatment assignment:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 and durvalumab 1125 mg IV infusion over approximately 1 hour on Day 15 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle.

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zoledronic acid, denosumab) is permitted as per the Investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the Sponsor.

During the study, subjects will have computed tomography (CT) scans every 42 days (-3/+7 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. Tumor evaluations will be assessed by the

investigative sites and response will be determined according to RECIST 1.1 guidelines, and immune-related RECIST criteria (irRECIST) when applicable. All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

4.1.2.1. Treatment Beyond Progression for Subjects in the *nab*-Paclitaxel/Durvalumab Arm

Subjects in the *nab*-paclitaxel/durvalumab arm may be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria
- Investigator assessed clinical benefit and absence of rapid disease progression or clinical deterioration
- Stable performance status
- Tolerance to IP
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, brain metastases)

Subjects will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomforts and other alternative treatment options.

Response assessment should continue every 42 days (-3/+7 days) as per Table of Events (Table 4). The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with *nab*-paclitaxel/durvalumab. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment and the subject consents, the subject may remain on the trial and will continue to receive monitoring according to the schedule in the Table of Events. The decision to continue treatment should be discussed with the Sponsor's Medical Monitor and documented in the study source documents.

Study therapy should be discontinued if further progression is documented by irRECIST.

4.1.3. End-of-Treatment Visit

The End-of-Treatment Visit is defined as the visit when decision for treatment discontinuation is made.

4.1.4. Follow-up Period

All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor will enter the Follow-up Period. It will consist of a visit 28 days after last dose of IP or End-of-Treatment Visit, whichever is later, followed by phone follow-up for survival approximately every 90 days (+/- 14 days) for at least 12 months after the last subject is randomized or 120 PFS events have been observed, whichever comes later, between the nab-paclitaxel/CC-486 combination and nab-paclitaxel monotherapy

arms. Subjects in the *nab*-paclitaxel/durvalumab arm will also attend a follow-up visit 90 days after the last dose of IP, and will be followed for survival in a similar manner for at least 12 months after the last subject is assigned to this arm. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. All post-treatment anticancer therapies will be recorded during the Follow-up Period.

4.2. Study Design Rationale

This is an open-label study designed to estimate the effects of adding CC-486 or durvalumab to *nab*-paclitaxel and *nab*-paclitaxel monotherapy in second/third-line NSCLC. A placebo-controlled study would not be feasible for this population as blinding would be difficult and would need a double dummy design.

A key objective in this study is to determine the chemo-priming effect of CC-486 and to estimate the effect of the combination of *nab*-paclitaxel with PD-L1 checkpoint inhibitor. Second/third-line NSCLC enables a unique setting to evaluate epigenetics:

a) It is currently unknown whether patients in second or later lines of treatment have optimal immune function/reserve which is critical for safety and activation of immune cells that target cancer cells,

b) Due to the overlapping (and dose-limiting) toxicities of doublet/triplet chemotherapy regimens in the first-line setting, it would be very challenging to combine epigenetic therapy at a dose level to elicit clinically meaningful benefit.

Although docetaxel has been assessed in other randomized studies as a chemotherapy backbone as shown in Table 3, the considerable neutropenia-related toxicity could potentially pose safety concerns if combined with CC-486, and the steroid premedication could confound the epigenetic impact of CC-486. In addition, the q3w dosing schedule of docetaxel restricts dose adjustment options, thus potentially yielding lower chemotherapy dose-intensity. As mentioned above, *nab*-paclitaxel has shown benefit for both squamous and nonsquamous histologies. Furthermore, recent data with immune checkpoint inhibitors (eg, nivolumab) have shown greater efficacy in subjects with squamous histology versus nonsquamous histology with manageable toxicities. Hence it will be important in the current study to assess the efficacy and safety of *nab*-paclitaxel either as monotherapy or in combination treatment in subjects with squamous and nonsquamous NSCLC histologies.

For patients with NSCLC whose disease progressed after initial chemotherapy, the goal of therapy is to delay further progression for as long as possible; hence, the use of PFS as the primary endpoint for efficacy evaluation.

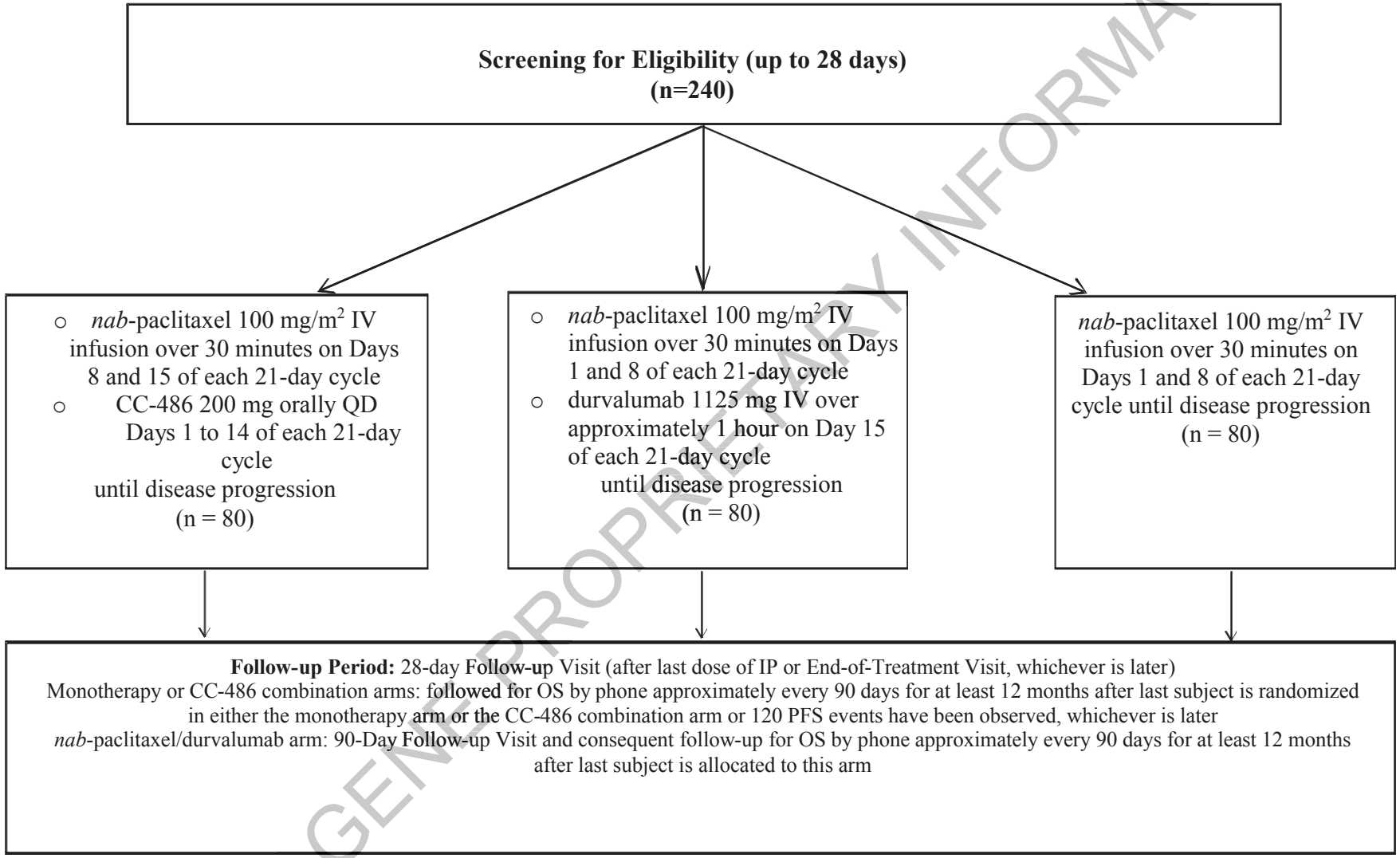
Table 3: Data for Control Arms using Taxanes from Phase II and III Studies Blinded

Study compound (year)	**Doce** (Shepherd, 2000)	**Doce** (Hanna, 2004)	***nab*-Pac** (Chen 2012, Saxena, 2012, Yuan 2012)	**Doce** (Reck, 2014a) LUME-1	**Doce** (Garon, 2014)	**Doce** (Brahmer, 2015) Checkmate 017	**Doce** (Borghaei, 2015) Checkmate 057	**Doce** (Vansteenkiste, 2015) POPLAR
Phase	**III**	**III**	**II**	**III**	**III**	**III**	**III**	**II**
N	55 + 48	288	16 (x2) - 33	272	625	137	290	143
Efficacy								
ORR (%)	7.1	8.8	18 - 33	3.3	14	9	12	15
SD rate (or DCR) (%)	42.7	46.4	31 - 42	37.9	53	34	33	n/a
PFS (TTP) (median, in months)	na	2.9	2.1 – 5.0	2.7	3.0	2.8	4.2	3.0
OS (median, in months)	7.0	7.9	n/a	9.1	9.1	6.0	9.4	9.7
Toxicity								
Neutropenia (%) Neutrophils decreased (%)	67.3	40.2	n/a	12.1 29.9	39	33	31	n/a
Febrile neutropenia	1.8	12.7	n/a	4.7	10	11	10	n/a
Thrombocytopenia (%)	0	0.4	3	NR	1	n/a	n/a	n/a
Anemia (%)	5.5	4.3	3	3.5	6	22	20	n/a
Peripheral Neuropathy (%)	1.8	1.1	3	NR	2	12	n/a	n/a
Fatigue / Asthenia (%)	18.2	5.4	3	5.1	10*	46.5	46.6	n/a

DCR = disease control rate; Doce = docetaxel; *nab*-Pac = *nab*-paclitaxel; N = number of subjects randomized; n/a = not available; ORR = overall response rate; OS = overall survival; PFS = progression free survival; SD = standard deviation; TTP = time to progression; *Grade ≥ 3.

Furthermore, maintaining quality of life during this period, especially in reducing/managing toxicity is also an important consideration. Therefore, the proposed study is designed to optimize the evaluation of efficacy with a tolerable dose/schedule of chemotherapy, and its combination with an epigenetic modifying therapy or with an immune checkpoint inhibitor.

Figure 2: Overall Study Design



IP = investigational product; IV = intravenous; OS = overall survival; PFS = progression-free survival; QD = once daily.

4.3. Study Duration

Recruitment is expected to take approximately 28 months, and the final analysis of PFS between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms will be performed when approximately 120 PFS events have occurred, estimated as approximately 25 months from first subject randomized. The final analysis for the *nab*-paclitaxel/durvalumab arm will be conducted when approximately 50 events have occurred in this arm. The total length of this Phase 2 study with follow-up is estimated to last approximately 40 months.

4.4. End of Trial

The End of Trial is defined as either the:

- date of the last visit of the last subject to complete the post-treatment follow-up, or
- date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

5. TABLE OF EVENTS

Table 4: Table of Events

Assessment	Screening/ Baseline	Treatment Period Every 21-day Cycle				End-of-Treatment/ Discontinu-ation Visit	Follow-Up Period		
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of IP)	90-day Follow-up Visit for subjects in the nab-paclitaxel/ durvalumab arm (after last dose of IP)	Survival Follow-up[a] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Informed Consent	X	-	-	-	-	-	-	-	-
Medical History (including Tobacco Exposure History), Prior Medication and Procedures	X	-	-	-	-	-	-	-	-
Serum β-hCG[b]	X	-	-	-	-	-	-	-	-
Urine Pregnancy Test[b]	-	X	-	-	-	X	X (nab-paclitaxel/ durvalumab arm)	X (nab-paclitaxel/ durvalumab arm)	-
Reminder to Avoid Pregnancy[b]		X	-	-	-	X	X	X	-
Complete Chest CT Scan and Any Other Studies Required for Tumor Imaging[c]	X	-	-	-	X	X[c]	-	-	X
Weight and Height[d]	X	X	X	X	-	-	-	-	-
ECOG Status	X	X	-	-	-	X	X	X	-
Concomitant Medication/Procedures	-	X	X	X	-	X	X	X	X
Peripheral Neuropathy Assessment[e]	X	X	-	-	-	X	X	-	-
Healthcare Resource Utilization Questionnaire	-	X	-	-	-	X	X	-	-
LCSS, EORTC QLQ C30 and EQ-5D-5L	-	X	-	-	-	X	X	-	-
Hematology[f,g]	X	X	X	X	-	X	X	X[k]	-

Table 4: Table of Events (Continued)

Assessment	Screening/ Baseline	Treatment Period Every 21-day Cycle				End-of-Treatment/ Discontinu-ation Visit	Follow-Up Period		
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of IP)	90-day Follow-up Visit for subjects in the nab-paclitaxel/ durvalumab arm (after last dose of IP)	Survival Follow-up[a] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Serum Chemistry[f,h]	X	X	-	-	-	X	X	X[k]	-
Archived Tumor Tissue Sample for Biomarker (biopsy, surgical specimen, or other diagnostic tumor sample)	-	X (C1D1 only)	-	-	-	-	-	-	-
Plasma for Biomarker Analyses	-	X (C1D1 only predose)	-	-	-	-	-	-	-
Blood for Pharmacogenomic Analyses	-	X (C1D1 only predose)	-	-	-	-	-	-	-
Adverse Event Evaluation in the Monotherapy or *nab*-Paclitaxel/CC-486 Combination Arm	After signing ICF and until 28 days after the last dose of IP							-	-
Adverse Event Evaluation in the *nab*-Paclitaxel/Durvalumab combination Arm	After signing ICF and until 90 days after the last dose of IP							X	-
nab-Paclitaxel Monotherapy Arm and *nab*-Paclitaxel/Durvalumab Combination Arm *nab*-Paclitaxel Administration/ Accountability[i]	-	X	X		-	-	-	-	-
nab-Paclitaxel/CC-486 Combination Arm *nab*-Paclitaxel Administration/ Accountability[i]	-	-	X	X	-	-	-	-	-

Table 4: Table of Events (Continued)

Assessment	Screening/ Baseline	Treatment Period Every 21-day Cycle				End-of-Treatment/ Discontinu-ation Visit	Follow-Up Period		
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of IP)	90-day Follow-up Visit for subjects in the nab-paclitaxel/ durvalumab arm (after last dose of IP)	Survival Follow-up[a] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
nab-Paclitaxel/CC-486 Combination arm CC-486 Administration/ Accountability[i]	-	X			-	-	-	-	-
nab-Paclitaxel/Durvalumab Combination Arm Durvalumab Administration/ Accountability[i]	-	-	-	X	-	-	-	-	-
Survival Phone Call	-	-	-	-	-	-	-	-	X[a]
Physical Examination[j]	X	X	-	-	-	X	-	-	-
Vital Signs[j]	X	X	X	X	-	X	-	-	-
Electrocardiogram (ECG)	X	Will be done as per standard of care during the Treatment Period and as clinically indicated; however, results will not be routinely collected in the eCRFs. If CT/bone scans show lesions pertinent for RECIST 1.1 or irRECIST criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs. If ECGs are abnormal and clinically significant, the data will be recorded on the AE/SAE eCRF.							
Bone Scan (X-rays if needed)	If clinically indicated								
CT Scan of the Head or Brain Magnetic Resonance Imaging (MRI)	If clinically indicated (mandatory if symptomatic)								

AE = adverse event; β-HCG = beta human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer QLQ C30; EQ-5D-5L = EuroQol 5D-5L; ICF = informed consent form; IP = investigational product; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; LCSS = Lung Cancer Symptom Scale; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

[a] Every 90 (+/-14) days (from 28-day Follow-up Visit) for at least 12 months after the last subject is randomized in either the monotherapy or the CC-486 combination arms or 120 PFS events have been observed whichever comes later. Subjects in the nab-paclitaxel/durvalumab arm will be followed for survival in a similar manner for at least 12 months after the last subject is assigned to this arm.

[b] All males and all women of child-bearing potential must be reminded to avoid pregnancy prior to administration of IP before beginning each new cycle, at the End-of-Treatment Visit and at the Follow-up Visits. 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/Baseline. Note: the screening serum pregnancy test can be used as the Cycle 1 Day 1 test prior to study therapy if it is

performed within the 72-hour timeframe. A urine pregnancy test must be performed prior to administration of IP before beginning each new cycle and at the End-of-Treatment Visit for all subjects, and at the Follow-up Visits for subjects in the *nab*-paclitaxel/durvalumab arm.

[c] All subjects must have a radiographically documented measurable tumor(s) by RECIST 1.1 criteria: Complete chest CT scan (including base of neck and adrenal gland) will be performed at Screening, every 42 days (-3/+7 days) (starting from Cycle 1 Day 1) until disease progression, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. The results of a complete chest CT scan (including base of neck and adrenal gland) performed per standard of care may be accepted and not repeated during Screening provided it was performed within 28 days of the first dose of IP (Cycle 1 Day 1). The methods of assessment chosen at baseline to follow tumors are to remain consistent throughout study duration. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. If the CT scan was performed within 2 weeks of the End-of-Treatment Visit, this End-of-Treatment Visit CT scan will not need to be repeated. Subjects in the *nab*-paclitaxel/durvalumab arm who continue beyond disease progression per RECIST 1.1 will continue to have CT scans every 42 days (-3/+7) until progression per immune-related RECIST criteria (irRECIST) version 1.1 (Nishino, 2013).

[d] Height will only be obtained at Screening Visit. Weight will be obtained at Screening and every visit during the Treatment Period before administration of IP.

[e] The occurrence of peripheral neuropathy will be reported by the Investigator per protocol as an AE or SAE.

[f] All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

[g] Hematology panel: hemoglobin, hematocrit, red blood cell count and morphology, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with absolute and differential and percent (neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands), platelet count, reticulocytes, erythrocyte sedimentation rate, international normalized ratio, prothrombin time, partial thromboplastin time, and fibrinogen. Additional laboratory samples for safety may be collected as clinically indicated.

[h] Serum chemistry panel: sodium, potassium, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, serum creatinine and clearance, uric acid, glucose, lactic dehydrogenase, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, total, direct and indirect bilirubin, ferritin, amylase, lipase, thyroid stimulating hormone (TSH), T4, free T3, and free T4. Additional laboratory samples for safety may be collected as clinically indicated.

[i] *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle; *nab*-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle; or *nab*-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 and durvalumab 1125 mg IV infusion over approximately 1 hour on Day 15.

[j] Physical examination and vital signs assessment should be performed prior to IP administration at these visits. Additional physical examination and vital signs assessments may be performed throughout the study as clinically indicated. Only abnormal and clinically significant physical examination data and/or vital signs will be recorded as an AE/SAE on the eCRF. Vital signs will be (at a minimum): blood pressure, heart rate, respiratory rate, body temperature.

[k] Hematology panel, serum chemistry will be performed at the 90-day Follow-up Visit for subjects in the *nab*-paclitaxel/durvalumab arm if applicable following AEs or abnormal assessments findings during the 28-day Follow-up Visit.

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. All subjects who sign an ICF must be entered into the Integrated Response Technology (IRT) immediately upon signature on the document. Subjects who do not meet the eligibility criteria will be considered screening failures and will not be eligible for the study. Subjects who fail initial screening may undergo re-screening up to 2 times at any time and an ICF will need to be resigned, as well as all screening procedures repeated (some procedures may not need to be done if previously done within 28 days prior to screening again). Subjects that have met all eligibility criteria after the Screening Period will be eligible for randomization /treatment assignment.

6.1. Medical History

A complete medical history including, but not limited to, evaluation for past (up to 5 years) or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatological, psychiatric, genitourinary, obstetrical, surgical history or any other diseases or disorders will be performed at Screening. All NSCLC-related medical history should be recorded regardless of time. Smoking status/tobacco exposure history will be captured on the eCRF.

6.2. Prior and Concomitant Medications and Procedures

Prior medications are defined as any medications started before randomization/treatment assignment. All NSCLC-related prior medications/procedures should be recorded regardless of time.

Concomitant medications are defined as any medication that was either initiated before randomization/treatment assignment and continued during the study treatment, or initiated on/after the date of randomization/treatment assignment and within 28 days after the last dose of IP for the monotherapy arm and the *nab*-paclitaxel/CC-486 combination arms, or 90 days after last dose of IP in the *nab*-paclitaxel/durvalumab combination arm.

All subjects will have concomitant medications and procedures (including radiation therapy) recorded at each visit from the time of signature on the ICF until the 28-day Follow-up Visit for the monotherapy arm and the *nab*-paclitaxel/CC-486 combination arms or 90 days after last dose of IP in the *nab*-paclitaxel/durvalumab combination arm, for conditions that are clinically significant or ongoing. During the Follow-up Period only NSCLC-associated concomitant medications/procedures (including radiation therapy) will be recorded, ie, subsequent-line(s) of anti-cancer therapy. Additionally, for laboratory procedures performed per standard of care during follow-up, laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF.

6.3. Pregnancy Testing

All males and all women of child-bearing potential must be reminded to avoid pregnancy prior to administration of IP before beginning each new cycle, at the End-of-Treatment Visit and at the Follow-up Visits. A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL must be performed to assess eligibility at Screening/Baseline. Note: the screening serum pregnancy test can be used as the Cycle 1 Day 1 test prior to study therapy if it is performed within the 72-hour timeframe. A urine pregnancy test must be performed prior to administration of IP before beginning each new cycle and at the End-of-Treatment Visit for all subjects, and at the Follow-up Visits for subjects in the *nab*-paclitaxel/durvalumab arm. 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 IP must be immediately reported to Celgene Drug Safety (See Section 11.4).

6.4. Complete Chest Computed Tomography (CT) Scan

A complete chest CT scan (including base of neck and adrenal gland) and any other studies required for tumor imaging will be done at Screening, every 42 days (-3/+7 days) (starting from Day 1 Cycle 1), and End-of-Treatment, until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. The results of a complete chest CT scan (including base of neck and adrenal gland) performed per standard of care may be accepted and not repeated during Screening provided it was performed within 28 days of the first dose of IP (Cycle 1 Day 1). Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor. If the CT scan was performed within 2 weeks of End-of-Treatment Visit, this End-of-Treatment CT scan will not need to be repeated. Additional CT scans may be done at any time during the study if clinically indicated. All CT scans and reports should be archived at the site according to site regulations and copies provided to the Sponsor if requested. All post-treatment anticancer therapies will be recorded during the Follow-up Period.

6.5. Weight and Height

Weight will be obtained at Screening and at every visit during the Treatment Period before administration of IP. Additional measurements of weight may be collected per local standards at any time during the study as needed. Height will only be collected at Screening. All weight and height data will be collected on eCRFs.

6.6. ECOG Performance Score

Eastern Cooperative Oncology Group performance status score will be collected at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the Follow-up Visits. Additional ECOG assessments may be performed at any time during the study as clinically indicated.

6.7. Peripheral Neuropathy Assessment

Peripheral neuropathy (sensory or motor) assessment will be done at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Changes in neuropathy grade from baseline will be reported as an AE as per Section 11. Additional peripheral neuropathy assessments may be done at any time during the study as clinically indicated.

6.8. Adverse Event Reporting

Adverse events will be recorded from time of signature on the ICF until 28 days after the last dose of IP for the monotherapy and the *nab*-paclitaxel/CC-486 combination arms and until 90 days after the last dose of IP for the *nab*-paclitaxel/durvalumab combination arm during the Follow-up Visits, including any unscheduled visits. See Section 11 for details.

6.9. Quality of Life Questionnaires

The LCSS, EORTC QLQ C30 and EQ-5D-5L questionnaires will be used to measure quality of life (QoL) for subjects in the study. The LCSS is comprised of 9 questions to be completed by the subject using a visual analogue scale (VAS) to denote intensity of a symptom. The EQ-5D-5L comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a VAS for overall QoL. These questionnaires will be completed by the subject prior to interaction with study personnel, at Day 1 of every Cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit.

6.10. Healthcare Resource Utilization Questionnaire

A healthcare resource utilization questionnaire 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 on Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit.

6.11. Laboratory Assessments

Blood for hematology and chemistry evaluation will be collected as per Table 4, Table of Events. Blood for hematology will be collected at Screening, Days 1, 8, and 15 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Blood for serum chemistry will be collected at Screening, Day 1 of every treatment cycle, at the End-of-Treatment Visit and at the 28-day Follow-up Visit. Hematology panel and serum chemistry will be performed at the 90-day Follow-up Visit for subjects in the *nab*-paclitaxel/durvalumab arm if applicable following AEs or abnormal assessments findings during the 28-day Follow-up Visit. Hematology panel will consist of: hemoglobin, hematocrit, red blood cell count and morphology, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with absolute and differential and percent (neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands), platelet count, reticulocytes, erythrocyte sedimentation rate, international normalized ratio, prothrombin time, partial thromboplastin time and fibrinogen. Serum chemistry panel includes: sodium, potassium, bicarbonate, calcium,

magnesium, phosphorus, blood urea nitrogen, serum creatinine and clearance, uric acid, glucose, lactic dehydrogenase, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, total, direct and indirect bilirubin, ferritin, amylase, lipase, thyroid stimulating hormone (TSH), T4, free T3, and free T4. Additional laboratory samples for safety may be collected as clinically indicated.

All scheduled laboratory samples will be sent to a central laboratory for analysis. Local hematology and chemistry tests may be performed as required for subject management/treatment decisions. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF (see Section 11.3).

Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or SAE (clinically significant laboratory abnormalities at Screening may result in a subject being ineligible for the study and should not be captured as an AE).

Any abnormal values that persist should be followed at the discretion of the Investigator. The Investigator should file all copies of the reports, including faxes with the subject's medical chart.

6.12. Tumor Tissue Sample Collection and Peripheral Blood Collection (Exploratory Assessments)

Histologically or cytologically confirmed advanced NSCLC is a required inclusion criteria for entry into this study. If a subject's previously collected tumor tissue (also known as archival tumor) is available, these samples will be collected for biomarker testing as detailed below at Cycle 1 Day 1. If such samples do not exist, have been depleted, or do not contain sufficient tumor material to be analyzed, this will not preclude participation in the study and a new biopsy or other procedure to collect tumor tissue will not be required. Table 5 delineates the specific requirements for commonly encountered archival tumor types.

Table 5: Requirements for Collection Based on Archival Tumor Sample Type

Sample Type	Amount to Collect	Collection Requirement for Biomarkers	Comments/ Exceptions
Core biopsy or surgical specimen	10 slides ≥4 µM thickness. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists.	If the quantity of material is not sufficient, the available amount will be collected.
Fine needle aspirates (FNA)	10 slides ≥4 µM. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists, unless a core biopsy or surgical sample was provided.	If the quantity of material is not sufficient, the available amount will be collected.
Transbronchial endoscopy samples	10 slides ≥4 µM. If a block is provided, a core of viable tumor will also be collected.	Mandatory if the sample exists, unless a core biopsy or surgical sample was provided.	If the quantity of material is not sufficient, the available amount will be collected.

Table 5: Requirements for Collection Based on Archival Tumor Sample Type (Continued)

Sample Type	Amount to Collect	Collection Requirement for Biomarkers	Comments/ Exceptions
Bronchial lavage, sputum, or other sample types	Slides or blocks representing >100,000 tumor cells	Collection is strongly encouraged when these samples contain sufficient material.	Collection is strongly encouraged when these samples contain sufficient material.

In addition, test results for tumor mutational status of genes, including but not limited to EGFR, ALK, KRAS and PD-L1 will be collected, if available from prior testing, and recorded on eCRF if these tests have been performed.

Plasma for cell-free nucleic acids analyses will be collected on Cycle 1 Day 1 prior to first dose of IP, as will a sample of whole blood or peripheral blood mononuclear cells for a germ-line reference comparison. Types of techniques planned to be used for tumor and plasma analyses include:

- Gene expression by RNA sequencing
- Immunohistochemistry
- DNA sequencing
- DNA methylation profiling

Details regarding the collection, storage, and shipment of the samples are given in the Laboratory Manual.

6.13. Electrocardiogram

Electrocardiograms (ECGs) will be done at Screening and as per standard of care during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal, changed and clinically significant, unless the finding is already documented in medical history.

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

A CT scan of the head, or preferably brain MRI, will be done as per standard of care at Screening (mandatory if symptomatic), during the Treatment Period, and as clinically indicated. If CT scans show lesions pertinent for RECIST 1.1 criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs.

6.15. Bone Scans and X-rays

Bone scans and x-rays will be done as per standard of care at Screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs. If bone scans or X-rays show lesions pertinent for RECIST 1.1 criteria evaluation, data will be collected on the pertinent tumor evaluation eCRFs.

6.16. Physical Examinations

Physical examinations will be done at Screening, on Day 1 of every treatment cycle, at the End-of-Treatment Visit, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.17. Vital Signs

Vital signs (at a minimum blood pressure, heart rate, respiratory rate and body temperature) will be done at Screening, prior to IP administration on Days 1, 8, and 15 of every treatment cycle, at the End-of-Treatment Visit, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.18. Survival

After the End-of-Treatment Visit, the subjects will have a 28-day Follow-up Visit followed by a phone call approximately every 90 days (+/- 14 days) for at least 12 months after the last subject is randomized in either the nab-paclitaxel/CC-486 combination therapy and nab-paclitaxel monotherapy arm or 120 PFS events have been observed between these two arms, whichever comes later. Subjects in the *nab*-paclitaxel/durvalumab arm will be followed for survival in a similar manner for at least 12 months after the last subject is assigned to this arm.

The subjects will also be asked questions about other medications they may be taking for their NSCLC. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the Sponsor.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Male and female subjects with advanced NSCLC who have received no more than one prior chemotherapy regimen for their advanced disease will be eligible for this study (immunotherapy in prior line of treatment is allowed, including platinum doublet combination). Subjects will receive study therapy as second or third line of treatment for advanced disease. The study will randomize/assign a maximum of approximately 240 subjects if all 3 arms proceed to the end of the study. The study will be conducted at approximately 40 sites in the US, Canada, and Europe.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be randomized/assigned in the study:

1. Age ≥ 18 years at the time of signing the ICF.
2. Understand and voluntarily provide written informed consent prior to the conduct of any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Histologically or cytologically confirmed advanced NSCLC who will receive study therapy as second- or third-line of treatment for advanced disease.
5. No other current active malignancy requiring anticancer therapy.
6. Radiographically documented measurable disease (defined by the presence of ≥ 1 radiographically documented measurable lesion).
7. One prior platinum-containing chemotherapy for metastatic or recurrent NSCLC, unless patients are ineligible to receive it or if disease progressed within 6 months of a platinum-containing neoadjuvant/adjuvant regimen. Patients may have received no more than one line of chemotherapy; immunotherapy in prior line of treatment (first or second line) is allowed.
8. Absolute neutrophil count (ANC) ≥ 1500 cells/mm3.
9. Platelets ≥ 100,000 cells/mm3.
10. Hemoglobin (Hgb) ≥ 9 g/dL.
11. Aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]) and alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × upper limit of normal range (ULN) or ≤ 5.0 × ULN if liver metastases.
12. Total bilirubin ≤ 1.5 ULN (unless there is a known history of Gilberts Syndrome).
13. Serum creatinine ≤ 1.5 x ULN, or calculated creatinine clearance ≥ 60 mL/min (if renal impairment is suspected 24-hour urine collection for measurement is required).
14. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
15. 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 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. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

b. Either commit to true abstinence* from heterosexual contact or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 3 months after discontinuation of study therapy.

Male subjects must:

a. 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 IP discontinuation, even if he has undergone a successful vasectomy.
b. Refrain from semen or sperm donation while taking durvalumab and for at least 3 months after the last dose of durvalumab.

16. Females must abstain from breastfeeding during study participation and 3 months after IP discontinuation.

7.3. Exclusion Criteria

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

1. Refractory to prior taxane therapy for advanced disease. Prior taxane used in the adjuvant setting does not exclude eligibility, provided there is no disease recurrence within 12 months upon completion of chemotherapy in that setting.
2. Evidence of active brain metastases, including leptomeningeal involvement (prior evidence of brain metastasis are permitted only if asymptomatic and clinically stable for at least 8 weeks following completion of therapy). MRI of the brain (or CT scan w/contrast) is preferred. Antiepileptic treatment is permitted in the context of prophylaxis for seizures.
3. Only evidence of disease is non-measurable at study entry.
4. Patients with known activating mutations in EGFR (such as exon 19 deletions or L858R).
5. Patients with known activating mutations in EML4-ALK.
6. Preexisting peripheral neuropathy of Grade ≥ 2 (per NCI CTCAE v4.0).

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

7. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
8. Venous thromboembolism within 1 month prior to Cycle 1 Day 1.
9. Current congestive heart failure (New York Heart Association Class II-IV).
10. History of the following within 6 months prior to Cycle 1 Day 1: 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 electrocardiogram (ECG) abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder.
11. Known hepatitis B or C virus (HBV/HCV) infection, known history of human immunodeficiency virus (HIV) infection, or receiving immunosuppressive or myelosuppressive medications that would in the opinion of the Investigator, increase the risk of serious neutropenic complications, history of active primary immunodeficiency, active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice).
12. 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.
13. Subject has a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies. Any lung disease that may interfere with the detection or management of suspected drug-related pulmonary toxicity.
14. Subject has a clinically significant malabsorption syndrome, persistent diarrhea, or known sub-acute bowel obstruction ≥ NCI CTCAE Grade 2, despite medical management.
15. Treatment with any chemotherapy, investigational product, biologic or hormonal therapy for cancer treatment within 28 days prior to signing the ICF. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
16. History of or suspected allergy to any IP or their excipients.
17. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
18. Currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices.
19. 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.
20. Any other malignancy within 5 years prior to randomization/treatment assignment, or advanced malignant hepatic tumors, with the exception of adequately treated 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 Classification of Malignant Tumours (TNM) stage of T1a or T1b). (All treatment of which should have been completed 6 months prior to signing ICF).

21. Radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting 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.
22. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
23. Any medical condition that confounds the ability to interpret data from the study.
24. Female patients who are pregnant or breastfeeding or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab.
25. Male patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab and from screening to 6 months after the last dose of *nab*-paclitaxel.
26. History of allogenic organ transplantation.
27. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea, systemic lupus erythematosus, sarcoidosis syndrome, or Wegener's syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (eg, following Hashimoto's syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
28. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

29. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.
30. Prior enrollment and treatment in a previous durvalumab clinical study.
31. Patients who have received prior anti-PD-1 or anti PD-L1:
    - Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
    - All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
    - Must not have experienced a ≥ Grade 3 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Subjects with endocrine AE of ≤ Grade 2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
    - Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

Subjects will receive open-label *nab*-paclitaxel / CC-486, *nab*-paclitaxel /durvalumab or *nab*-paclitaxel monotherapy during the Treatment Period of the study. *nab*-paclitaxel, durvalumab and CC-486 are designated as IP and will be packaged and supplied by the study Sponsor.

The reconstitution and IV administration of *nab*-paclitaxel should follow the local Prescribing Information for Abraxane®.

8.1.1. *nab*-Paclitaxel

nab-Paclitaxel will be supplied by the Sponsor in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and 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. Reconstituted *nab*-paclitaxel should be stored in an area accessible only to study personnel.

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

8.1.2. CC-486 (Azacitidine for Oral Administration)

The Sponsor will supply azacitidine 100 mg tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed. CC-486 may be taken on an empty stomach or with food. Subjects should drink 8 ounces (240 mL) of room temperature water with each dose. It is strongly recommended that all subjects receive a dose of a prophylactic antiemetic, preferably a 5-HT3 antagonist, approximately 30 minutes prior to each dose of CC-486.

The IP must be stored as directed on package label at controlled temperature and a temperature log must be maintained in the source documents. The storage area should be secure and have access limited to study personnel.

8.1.3. Durvalumab (MEDI4736)

Durvalumab will be supplied by the Sponsor in single use vials in single count cartons. Each 10R (10 mL) vial will be supplied as a liquid solution containing 500 mg (nominal) of IP at a concentration of 50 mg/mL. Durvalumab should be stored in accordance with the product label.

The study site is to supply the following:

- IV infusion bags of normal saline (0.9% [w/v] sodium chloride injection, 250 mL size). Saline bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride. Infusion lines should contain a 0.2-µm in-line filter.

- Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-μm in-line filter.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the MEDI4736 vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

For additional information on preparation and storage please refer to the pharmacy manual.

8.1.4. Monitoring During/After Durvalumab Infusion

First durvalumab infusion

On the first infusion day, subjects in the *nab*-paclitaxel/durvalumab combination arm will be monitored, and assessments collected/recorded in the eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

Blood pressure (BP) and pulse will be collected from subjects before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent durvalumab infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Subjects should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

For all infusions

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of IP may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate.

Acetaminophen/paracetamol and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥ Grade 3 or higher in severity, IP will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

8.2. Treatment Administration and Schedule

Following administration of *nab*-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

Once randomized (or assigned), subjects will be treated with *nab*-paclitaxel / CC-486, *nab*-paclitaxel / durvalumab or *nab*-paclitaxel monotherapy until disease progression, development of an unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the Sponsor:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 and durvalumab 1125 mg IV infusion over approximately 1 hour on Day 15 of each 21-day treatment cycle, or
- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

8.3. Dose Omissions and Modifications

8.3.1. Rules for Dose Omissions and Modified Schedules

nab-Paclitaxel Monotherapy Arm

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

- **Day 1 Dose Missed**

If *nab*-paclitaxel cannot be administered on Day 1 within the 2 days allowable window,

- ✓ *nab*-paclitaxel may not be skipped but only delayed
- ✓ Delay of Day 1 will automatically shift the following visit for this cycle

- **Day 8 Dose Missed**

If the *nab*-paclitaxel dose for Day 8 is given >9 days from Day 1, the Day 8 dose, when administered, can be either considered as delayed or skipped, depending on the intention of the Investigator.

- ✓ *nab*-paclitaxel may be delayed up to Day 15: this dose will be considered as delayed Day 8; the next visit will be the planned Day 1 of the next cycle which will not be automatically pushed back
- ✓ *nab*-paclitaxel may be skipped: if the second *nab*-paclitaxel dose cannot be given in a cycle it may be skipped; the next dose would be administered as the Day 1 dose

nab-Paclitaxel/CC-486 Combination Arm

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

If any doses of CC-486 are missed, skip that day and resume as appropriate, do not double up on subsequent days.

- **Day 1 Dose Missed**

If CC-486 cannot be administered on Day 1 within the 2 days allowable window,

- ✓ The *nab*-paclitaxel Day 8 dose would not necessarily be pushed back / delayed
- ✓ Doses of CC-486 would be skipped (exposure to CC-486 would be reduced on that cycle).

For hematologic toxicity, dosing should be reassessed at the next visit on Day 8.

- **Day 8 Dose Missed**

If *nab*-paclitaxel cannot be administered on Day 8 within the 2 days allowable window,

- ✓ *nab*-paclitaxel may be delayed (eg, for neuropathy): this dose will be considered as delayed Day 8; the next dose (Day 15) may also be delayed up to the original Day 1 of the next cycle (approximately 20 days from Day 1 of this cycle) to maintain the protocol specified visit gap
- ✓ *nab*-paclitaxel may be skipped (eg, hematotoxicity); the next dose would be administered as the Day 15 dose

If the dose for Day 8 is given > 9 days from Day 1, the Day 8 dose, when administered, can be either considered as delayed or skipped, depending on the intention of the Investigator.

Upon resuming treatment after stopping both IPs on adjusted Day 8, consideration for *nab*-paclitaxel resumption should take priority.

- **Day 15 Dose Missed**

If *nab*-paclitaxel cannot be administered on Day 15 within the 2 days allowable window,

- ✓ *nab*-paclitaxel may be delayed: this dose will be considered as delayed Day 15 (up to Day 1 of the next cycle); CC-486 may be started on Day 1 as planned

- ✓ If the *nab*-paclitaxel dose cannot be administered within 14 days from the last dose, it will be considered as skipped

nab-Paclitaxel/Durvalumab Combination Arm

No dose reductions of durvalumab are allowed. In case of doubt, the Investigator should consult with the Study Physician.

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered plus or minus 2 days from the scheduled date.

- **Day 1 Dose Missed**

If *nab*-paclitaxel cannot be administered on Day 1 within the 2 days allowable window,

- ✓ *nab*-paclitaxel may not be skipped but only delayed
- ✓ Delay of Day 1 will automatically shift the following visit for this cycle

- **Day 8 Dose Missed**

If the *nab*-paclitaxel dose for Day 8 is given > 9 days from Day 1, the Day 8 *nab*-paclitaxel dose should be skipped

- **Day 15 Dose Missed**

If durvalumab cannot be administered on Day 15 within the 2 days allowable window,

- ✓ Durvalumab may be delayed: this dose will be considered as delayed Day 15
- ✓ If the durvalumab dose cannot be administered within 14 days from the last dose, it will be considered as skipped

8.3.2. Rules for Dose Modifications

Subjects who experience any of the adverse drug reactions in Table 6 will be dose reduced as per Table 6 during treatment.

nab-Paclitaxel Monotherapy Arm

- Do not administer *nab*-paclitaxel on Day 1 of a cycle 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 withhold treatment 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, permanently reduce *nab*-paclitaxel doses as outlined in Table 6.
- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy. Resume *nab*-paclitaxel at reduced doses (Table 6) when peripheral neuropathy improves to Grade 1 or completely resolves.
    - For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to

the guidelines in Table 6. For any other Grade 3 or 4 nonhematologic toxicity or other Investigator defined unacceptable toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 6.

Re-escalation is not permitted at any time.

nab-Paclitaxel/CC-486 Combination Arm

- Do not administer *nab*-paclitaxel on Day 8 or CC-486 on Day 1 or 8 of a cycle 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 thrombocytopenia, withhold treatment until counts recover to a platelet count of at least 100,000 cells/mm^3 on Days 1 and 8 for CC-486 and Day 8 for *nab*-paclitaxel or to a platelet count of at least 50,000 cells/mm^3 on Day 15 of the cycle for *nab*-paclitaxel. Upon resumption of dosing, permanently reduce *nab*-paclitaxel and/or CC-486 doses as outlined in Table 6.
- In subjects who experience Grade ≥ 3 neutropenia, withhold treatment and start G-CSF treatment daily until the ANC ≥ 2000/mm^3 (please refer to Section 9.3 for G-CSF administration). Upon resumption, permanently reduce *nab*-paclitaxel and/or CC-486 dose as outlined in Table 6.
- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy (CC-486 does not need to be withheld). Resume *nab*-paclitaxel at reduced doses (Table 6) when peripheral neuropathy improves to Grade 1 or completely resolves.
- For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 6. For any other Grade 3 or 4 nonhematologic toxicity or other Investigator defined unacceptable toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 6.

Re-escalation is not permitted at any time.

nab-Paclitaxel/Durvalumab Combination Arm

Guidelines for the management of toxicities for durvalumab and *nab*-paclitaxel are provided in Appendix C.

In addition:

- Do not administer *nab*-paclitaxel on Day 1 of a cycle 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 withhold treatment 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, permanently reduce *nab*-paclitaxel doses as outlined in Table 6.

- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy. Resume *nab*-paclitaxel at reduced doses (Table 6) when peripheral neuropathy improves to Grade 1 or completely resolves.
- For Grade 2 or 3 cutaneous toxicity, Grade 3 mucositis, or Grade 3 diarrhea, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 6. For any other Grade 3 or 4 nonhematologic toxicity or other Investigator defined unacceptable toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 6.

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the durvalumab containing regimen by the reporting Investigator.

Treatment modifications referring to 'study regimen or treatment' would apply to both *nab*-paclitaxel and durvalumab unless AEs are not considered causally related to *nab*-paclitaxel by the reporting Investigator. In that case *nab*-paclitaxel or durvalumab treatment may be continued alone if deemed beneficial to the patient per Investigator's assessment.

Re-escalation is not permitted at any time.

Table 6: Permanent Dose Reductions for Hematologic and Nonhematologic Toxicities and Dosing on the Study

Dose Modification During Treatment			
Adverse Drug Reaction	**Occurrence**	**Monotherapy Arm: *nab*-paclitaxel Dose (mg/m^2)**	**Combination Arm: *nab*-paclitaxel Dose (mg/m^2) / CC-486 Dose (mg)**
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	100/100
	Second	50	75/100
	Third	Discontinue Treatment*	50/100
	Fourth	NA	Discontinue Treatment*
Platelet count < 50,000/mm^3	First	75	100/100
	Second	Discontinue Treatment*	75/100
	Third	NA	Discontinue Treatment*
Peripheral Neuropathy Grade ≥ 3	First	75	75/200
	Second	50	50/200
	Third	Discontinue Treatment*	
Grade 2 or 3 Cutaneous toxicity Grade 3 Diarrhea Grade 3 Mucositis Any other Grade 3 or 4 nonhematologic toxicity or other Investigator defined unacceptable toxicity	First	75	100/100
	Second	50	75/100
	Third	Discontinue Treatment*	50/100
	Fourth	NA	Discontinue Treatment*
Grade 4 Cutaneous toxicity, Diarrhea or Mucositis	First	Discontinue Treatment*	

ANC = absolute neutrophil count; AUC = area under the curve; NA = not applicable.
* If an adverse event that requires dose reduction recurs after the dose has been reduced according to the table above, the subject should generally 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

The Treatment Period of the study is open-label. Randomization/treatment assignment has been and will be carried out centrally using an IRT system.

8.5. Packaging and Labeling

The label(s) for all IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP 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.

8.6. Investigational Product Accountability and Disposal

The Sponsor (or its designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus the responsibilities of the Sponsor (or designee).

The Sponsor will instruct the Investigator on the return, disposal and/or destruction of IP. Only completely unused IP vials should be retained by the site until a representative from the Sponsor or other Sponsor-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 Drug Accountability Record Form.

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused CC-486 must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Sponsor representative (or its designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Sponsor representative (or its designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining IP will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Sponsor representative (or its designee). The Sponsor representative (or its designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the Investigator study file and the central clinical study file.

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 IP between locations within their network as clinical trial agreement and local guidelines permit.

8.7. Investigational Product Compliance

All IP will be administered only by study site personnel and accurate recording of all IP 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, CC-486, or durvalumab dosing.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of *nab*-paclitaxel, durvalumab or CC-486 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. For *nab*-paclitaxel, an infusion completed in less than 25 minutes may increase C_{max} by approximately 20%, therefore a *nab*-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the AE case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease recurrence. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zoledronic acid, denosumab) is permitted as per the Investigator's discretion and should be administered according to local institutional practice. All concomitant treatments, including blood and blood products, must be reported on the eCRF.

- Antiemetics are not required during the study; however, it is strongly recommended that all subjects receive a dose of a prophylactic antiemetic, preferably a 5-HT3 antagonist, approximately 30 minutes prior to each dose of CC-486.
- Stable, therapeutic doses of anticoagulants are permitted; however, subjects on warfarin should have prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) monitored as clinically indicated.
- Subjects on erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting the IP may continue their pretreatment doses throughout the study.
  - Note: If the subject is not on a stable dose of an erythropoiesis-stimulating agents (ESA) prior to study entry, the subject may not start an ESA during Cycle 1. However, medications such as ESAs, granulocyte colony-stimulating factors (G-CSFs), etc., may be administered according to standard of care after Cycle 1.
- Use of white blood cell growth factors (eg, filgrastim, G-CSF for the treatment of subjects with neutropenic fever is permitted at the Investigator's discretion. Use of filgrastim rather than pegylated-filgrastim is indicated, because of the 14 day delay of the next cycle following treatment with peg-filgrastim.
- Use of white blood cell growth factors (eg, filgrastim, G-CSF) for secondary prophylaxis in subjects who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received) is permitted.
- Flu vaccination with inactivated virus is permitted.
- Routine infectious disease prophylaxis is not recommended, however, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the Investigator.
- Treatments with bisphosphonates (eg, pamidronate, zoledronate), or other agents (eg, denosumab) to prevent or delay progression of bone metastases are permitted. Maintenance of a stable dosing regimen throughout the study is recommended.
- Subjects may receive physiologic replacement doses of glucocorticoids as maintenance therapy for adrenal insufficiency. Glucocorticoids may be administered as an antiemetic with IV chemotherapy, if directed by local standard of care. Use of immunosuppressive medications for the management of durvalumab-related AEs, or

in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

- Treatment with antidiarrheal medications is recommended at the first sign of diarrhea as per the guidelines in Appendix B. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate.
- The potential drug-drug interactions precautions contained in the *nab*-paclitaxel prescribing information will be applied to this study, unless otherwise specified in the protocol. Specifically, the metabolism of paclitaxel is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4. Caution is recommended when administering *nab*-paclitaxel concomitantly with medicines known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4. For information regarding other drugs that may interact with either *nab*-paclitaxel or durvalumab and affect their metabolism, pharmacokinetics, or excretion, please see the respective IP product information (refer to Prescribing Information and/or IB).
- Antiepileptic treatment is permitted, in the context of prophylaxis for seizures, for subjects with prior evidence of brain metastasis (asymptomatic and clinically stable for at least 8 weeks following completion of therapy for brain metastasis).

9.2. Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is enrolled in the study. Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery) other than the study treatments must not be given to subjects during the study. If such treatment is required, the subject must be discontinued from the study. Focal palliative radiotherapy for treatment of cancer-related symptoms is allowed during study treatment at the discretion of the Investigator. The administration of either α-interferon and/or ribavirin, or drugs with known renal toxicity is prohibited during study treatment. Monoclonal antibodies against CTLA-4, PD-1 or PD-L1 should not be given concomitantly.

Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers should not be given during the study unless required for management of immune-related toxicities (Appendix C).

Live attenuated vaccines should not be given through 30 days after the last dose of IP.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) EGFR TKIs should not be given concomitantly with durvalumab, and should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

9.3. Required Concomitant Medications and Procedures for Subjects Receiving CC-486

Data regarding G-CSF administration should be recorded on the eCRF provided for G-CSF administration.

9.3.1. Description of G-CSF

This medication stimulates the blood system (bone marrow) to make white blood cells, helping fight infections. This medication is given to those whose ability to make white blood cells has been reduced. Filgrastim (also known as G-CSF, or granulocyte colony stimulating factor) is a man-made version of a certain natural substance found in the body. It is produced using a certain bacteria. It will be obtained commercially and relabeled as clinical supplies. It should be stored, and administered according to the manufacturer's recommendation.

9.3.2. Administration of G-CSF

For subjects who experience Grade ≥ 3 neutropenia, G-CSF 5 μg/kg daily will be administered subcutaneously. During any cycle when Grade ≥ 3 neutropenia occurs, CC-486 and other cytotoxic agents will be held, and G-CSF will begin immediately (a minimum of 24 hours after the last dose of CC-486 and chemotherapy). In subsequent cycles, G-CSF will begin on Day 16. G-CSF will continue daily until the ANC ≥ 2000/mm^3. In subjects receiving G-CSF, the next cycle should begin no sooner than 48 hours after discontinuation of G-CSF.

For complete details on drug administration, storage, clinical pharmacology, and the human PK of G-CSF (filgrastim), please see the G-CSF (filgrastim) package insert.

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 statistical analysis plan (SAP). The SAP supersedes the analyses described in the protocol should there be differences between the two.

Evaluations of the study endpoints will be based primarily on the point estimates and the associated 95% confidence intervals of the within- and between-treatment differences.

10.1. Overview

Approximately 240 subjects will be assigned 1:1:1 to one of the three treatment arms (approximately 80 subjects per group). The combination arms will receive *nab*-paclitaxel with epigenetic modifying therapy of CC-486 or *nab*-paclitaxel with immunotherapy of durvalumab, and the monotherapy arm will receive *nab*-paclitaxel alone. All regimens will be administered in 21-day cycles. All subjects will receive the assigned study treatment until disease progression, unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the Sponsor, in accordance with local standard of care. Treatment beyond progression defined by RECIST 1.1 will be permitted per irRECIST criteria for those subjects in the *nab*-paclitaxel/durvalumab arm (see Section 4.1.2.1).

Prior to Protocol Amendment 4.0, all subjects were randomized 1:1 to the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms using a permuted-block randomization method with the following baseline stratification factors:

- ECOG performance status (0 versus 1)
- Gender (males versus females)
- Smoker (yes versus no)

Randomization was carried out centrally using an IRT system. As Protocol Amendment 4.0 implementation was in effect after enrollment completed in the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms (with each arm reaching a total of approximately 80 subjects), all subjects enrolled while Protocol Amendment 4.0 is in effect and at the time of Protocol Amendment 5.0 implementation will be assigned to the *nab*-paclitaxel/durvalumab combination therapy arm until approximately 80 subjects have been enrolled in that arm. Hence, treatment assignment of subjects to the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms was in effect conducted completely in a randomized fashion and randomization between the *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms will not apply.

A data monitoring committee (DMC) will be used to review the safety and efficacy data during the study.

10.2. Study Population Definitions

10.2.1. Intent-to-treat Population

The primary efficacy analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized (assigned) subjects regardless of whether the subject receives any IP or has any efficacy assessments performed.

10.2.2. Per-protocol (PP) Population

The PP population is defined as all eligible subjects randomized/assigned who receive at least one dose of the IP, have been treated in the arm they were assigned and meet the major eligibility criteria of the protocol. Additional analyses utilizing the PP population will be described in the SAP.

10.2.3. Treated Population

The treated population will consist of all randomized/assigned subjects who receive at least one dose of IP. The safety analyses will be based on the treatment as received if different from the assigned treatment by randomization/treatment assignment.

10.3. Sample Size and Power Considerations

The primary objective of this study is to estimate the efficacy of the *nab*-paclitaxel/CC-486 combination therapy, that of the *nab*-paclitaxel/durvalumab combination therapy, and that of the *nab*-paclitaxel monotherapy.

A secondary efficacy objective is to estimate the relative efficacy of each of the combination regimens to the *nab*-paclitaxel monotherapy regimen.

The effect of the treatment regimens with respect to the efficacy endpoints will be based on the point estimates and the associated 95% confidence intervals. The sample size was chosen to support the estimation of the within- treatment effects with reasonable precision. In the durvalumab arm, a sample size of 80 subjects will further allow the estimation of the treatment effect with reasonable precision when stratification by prior checkpoint inhibitor exposure (checkpoint naïve and prior exposure to checkpoint inhibitors) is performed.

No inferential statistical tests will be performed and no multiplicity adjustments are planned for the statistical analyses.

Table 7 below summarizes the two-sided 95% confidence intervals for a range of hypothetical observed disease control rates given a sample size of 80 subjects in a treatment arm. If the observed disease control rate is 0.30, then the actual width of the 2-sided 95% confidence interval is 0.21 (95% CI is [0.20, 0.41]).

Table 7: Disease Control Rate –Two-Sided 95% Confidence Interval of Hypothetical Disease Control Rate with a Sample Size of 80 Subjects in a Treatment Arm

Hypothetical Observed Disease Control Rate	Actual Width of 95% Confidence Interval	95% Confidence Interval[a]
0.20	0.186	(0.119, 0.304)
0.25	0.199	(0.16, 0.359)
0.30	0.21	(0.203, 0.413)
0.35	0.218	(0.247, 0.465
0.40	0.224	(0.292, 0.516)
0.45	0.227	(0.338, 0.565)
0.50	0.228	(0.386, 0.614)

[a] Based on the Clopper-Pearson exact method.

The between-treatment effect with respect to PFS can be estimated based on the point estimate of the hazard ratio and the associated 95% confidence interval. Table 8 below summarizes the precision that can be achieved given different scenarios of hypothetical observed hazard ratios between the treatment arms for PFS events, assuming a total of 120 events are observed.

Table 8: Progression-Free Survival – Two-Sided 95% Confidence Interval of Hypothetical Observed Hazard Ratio between Treatment Arms

Hypothetical Number of Events Observed	Hypothetical Observed Hazard Ratio of PFS Events	95% Confidence Interval of Hazard Ratio[a]
120	0.60	(0.42, 0.86)
	0.65	(0.45, 0.93)
	0.70	(0.49, 1.00)

[a] Assuming a standard error of 0.18 [estimated based on $(4/120)^{1/2}$] for the log hazard ratio.

Assuming the median times of PFS are 4.17 and 2.5 months, respectively, for the *nab*-paclitaxel/CC-486 combination therapy and *nab*-paclitaxel monotherapy arms, and an approximate 23 months accrual period for a total of 160 subjects, it is estimated that a total of 120 PFS events will have been observed approximately 2 months after the last subject is randomized to these 2 arms, assuming an exponential distribution for PFS. The final analysis of the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms will be performed when a total of approximately 120 PFS events have been observed between these two arms.

While there is published data demonstrating efficacy of *nab*-paclitaxel as monotherapy in a second line setting in advanced NSCLC with ORR ranging from 16.1 to 33% and a median PFS of up to 5 months, it is difficult to place an assumed treatment effect on *nab*-paclitaxel as a monotherapy (Chen, 2012; Saxena, 2012; Yuan, 2012). The assumption of 2.5 months PFS in the monotherapy arm is in line with this data and other efficacy data previously observed

following monotherapy treatment of advanced disease with other agents (Shepherd, 2000; Hanna, 2004; Reck, 2014; Garon, 2014).

[Of note, with 120 PFS events, this study has an 80% power (1-sided, Type-1 error of 2.5%) to detect a HR of 0.60 for PFS between two treatment arms.]

Assuming the median time of PFS is 4.25 months for the *nab*-paclitaxel/durvalumab combination therapy, and an approximate 13 months accrual period for a total of approximately 80 subjects, it is estimated that a total of approximate 50 PFS events will have been observed at approximately 3 months after the last subject is assigned to this arm, assuming an exponential distribution for PFS. The final analysis for PFS for the *nab*-paclitaxel/durvalumab arm will be performed when approximately 50 PFS events have been observed in this arm.

One nonbinding interim analysis for PFS with an early stopping rule for futility between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms will be conducted when approximately 60 events have been observed. The *nab*-paclitaxel/CC-486 combination arm may be stopped early for futility if the observed HR is > 1.10, and/or if recommended by the DMC based on the safety profile of this combination regimen. A HR> 1.10 when half of the target events of 120 have occurred signals a low probability for observing a meaningful difference in favor of the *nab*-paclitaxel/CC-486 combination therapy should the study continue to the end. With the assumptions stated above, it will take approximately 15 months from the first subject randomized to observe approximately 60 PFS events for the interim analysis.

An additional interim analysis for futility with the PFS endpoint between the *nab*-paclitaxel/durvalumab combination therapy and *nab*-paclitaxel monotherapy arms will be conducted when approximately 30 PFS events have been observed in the *nab*-paclitaxel/durvalumab combination arm. It is projected that 60 or more PFS events will have been observed in the *nab*-paclitaxel monotherapy arm at that point. The *nab*-paclitaxel/durvalumab combination arm may be stopped early for futility if the observed HR is ≥ 1.10, and/or if recommended by the DMC based on the safety profile of this combination regimen. With the assumptions stated above, it will take approximately 13 months from the first subject randomized to the *nab*-paclitaxel/durvalumab arm to observe the events needed for this interim analysis. As the enrollment in the *nab*-paclitaxel/durvalumab combination arm started after the enrollment in the *nab*-paclitaxel/CC-486 and *nab*-paclitaxel monotherapy arms ended, randomization between the *nab*-paclitaxel monotherapy and *nab*-paclitaxel/durvalumab arms does not apply. Nevertheless, the futility boundary for the interim analysis between the two arms will still be utilized as a guidance to the DMC for their recommendations.

At the interim analysis data review on , based on the recommendation of the DMC, treatment with CC-486 was discontinued in the *nab*-paclitaxel/CC-486 combination arm; subjects in this arm may be allowed to continue on *nab*-paclitaxel single agent, at the Investigator's discretion.

Similarly, following the outcome of the interim analysis between *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms, and taking into account the DMC recommendations, subjects may be allowed to remain on either *nab*-paclitaxel or durvalumab as a single agent or both agents, at the Investigator's discretion.

Disease control rate, OS, and ORR within and the difference between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy treatment arms will be estimated at the time of the

final analysis of the PFS endpoint when approximately 120 PFS events have been observed between these two arms. The same endpoints will be estimated within the *nab*-paclitaxel/durvalumab arm and between this and the *nab*-paclitaxel monotherapy arms when approximately 50 PFS events have been observed in the *nab*-paclitaxel/durvalumab arm.

All subjects in the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms will continue to be followed for OS for at least 12 months after the last subject is randomized to either of these two arms or 120 PFS events have been observed between these two arms, whichever comes later. All subjects in the *nab*-paclitaxel/durvalumab arm will be followed for OS for at least 12 months after the last subject is assigned to this arm.

The study milestones for the scenario that all 3 arms proceed to the end of the study are summarized in the table below:

Study Milestone	**Time from First Subject Randomized (Day 1)**
First subject randomized to either the *nab*-paclitaxel/CC-486 and *nab*-paclitaxel monotherapy arms (1:1 randomization ratio)	Day 1
Interim analysis for *nab*-paclitaxel/CC-486 vs. *nab*-paclitaxel monotherapy (~60 PFS events total)	~ 15 months
Addition of the *nab*-paclitaxel/durvalumab arm to the study; randomization in a 1:1:1 ratio to the *nab*-paclitaxel/CC-486, *nab*-paclitaxel/durvalumab, and *nab*-paclitaxel arms begins.	~ 15 months
Last subject randomized to the *nab*-paclitaxel/CC-486 and *nab*-paclitaxel arms	~ 23 months
Assignment of all incoming subjects to the durvalumab arm begins.	~ 24 months
Final analysis for *nab*-paclitaxel/CC-486 vs. *nab*-paclitaxel (~120 PFS events total)	~25 months
Last subject assigned to the *nab*-paclitaxel/durvalumab arm	~ 28 months
Interim analysis for *nab*-paclitaxel/durvalumab vs. *nab*-paclitaxel (~30 PFS events from *nab*-paclitaxel/durvalumab, ≥60 from *nab*-paclitaxel monotherapy)	~28 months
Final analysis for *nab*-paclitaxel/durvalumab vs. *nab*-paclitaxel (~50 PFS events have been observed in the *nab*-paclitaxel/durvalumab arm)	~ 31 months
End of OS Follow-up for subjects in *nab*-paclitaxel/CC-486 and *nab*-paclitaxel arms	~ 35 months
End of OS Follow-up for durvalumab subjects	~40 months

10.4. Background and Demographic Characteristics

The baseline characteristics of all randomized/assigned 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.

10.6. Efficacy Analysis

10.6.1. Primary Efficacy Endpoints

The primary efficacy endpoint is progression-free survival, which is defined as the time from the date of randomization/treatment assignment to the date of disease progression or death (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 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of study therapy.

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 are alive and drop out early without any post baseline radiologic tumor assessment will be censored on the date of randomization/treatment assignment.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time (including two-sided 95% CI) for each treatment arm. The Kaplan-Meier curve for PFS will be presented graphically for each treatment arm. The relative treatment effect between the combination and monotherapy arms on PFS will be estimated by the hazard ratio (HR) and the associated two-sided 95% CIs using the stratified Cox proportional hazard model with ECOG performance status (0 versus 1), gender (males versus females), and smoker (yes versus no) as the stratification factors, given the number of events in each cell is adequate. No statistical inferential tests will be performed.

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 for each treatment arm. In addition, confirmatory and sensitivity analyses may be

performed to further assess the impact of missed radiologic assessments. An additional analysis of PFS, where death or new treatment will be considered as an event, will be conducted to address the impact of next line therapy.

To explore the effect of treatment post initial progression, PFS defined by irRECIST criteria may be estimated for the subjects in the *nab*-paclitaxel/durvalumab arm.

10.6.2. Secondary Efficacy Endpoints

10.6.2.1. Disease Control Rate

Disease control rate is defined as the percent of subjects who have a radiologic complete response, partial response, or stable disease according to RECIST 1.1 guidelines, as determined by the Investigator.

Disease control rate for each treatment arm will be summarized by the observed DCR rate and the associated two-sided 95% CI. The relative treatment effect will be summarized by the absolute difference and ratio of the response rates and the associated two-sided 95% CI.

10.6.2.2. Overall Survival

Overall survival is defined as the time between randomization/treatment assignment 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 receiving treatment as of the data cutoff date will be censored at the cutoff date. Overall survival will be analyzed in a similar manner as that for PFS.

10.6.2.3. Overall Response Rate

Overall response rate is defined as the percent of subjects who have a radiologic complete or partial response according to RECIST 1.1 guidelines determined by the Investigator.

Overall response rate will be assessed using the same statistical methods as those for the DCR endpoint.

10.6.3. Exploratory Endpoints

10.6.3.1. HealthCare Utilization

Healthcare utilization will be summarized by treatment. Additional analyses will be described in detail in the SAP.

10.6.3.2. Quality of Life Questionnaires

The score or VAS value and the corresponding change from baseline at each timepoint will be summarized by treatment for the EQ-5D-5L, EORTC QLQ C30 and LCSS questionnaires. Additional analyses will be described in detail in the SAP.

10.6.3.3. Biomarker, Tumor Characteristics, and Genomic Analyses

Statistical analysis of the biomarkers, tumor characteristics, and genomic correlates will be described in a SAP separate from that described above.

10.6.3.4. Anti-tumor Activity and PD-L1 Expression (*nab*-Paclitaxel/Durvalumab Arm)

An exploratory analysis of PFS and DCR using investigator's assessments based according to irRECIST criteria, and their association with PD-L1 expression will be performed for subjects in the *nab*-paclitaxel/durvalumab arm.

10.7. Safety Analysis

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

The safety/tolerability of the treatment arms will be monitored through continuous reporting and evaluated by adverse events and serious adverse events, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of IP.

10.7.1. Adverse Events

TEAEs will be defined as any AE or SAE occurring or worsening on or after the day of the first dose of the IP through 28 days after the last dose of IP for the monotherapy arm and the *nab*-paclitaxel/CC-486 combination arms, or 90 days after last dose of IP in the *nab*-paclitaxel/durvalumab combination arm. In addition, any serious AE with an onset date more than 28 days after the last dose of IP that is assessed by the Investigator as related to IP will be considered a TEAE. TEAEs occurring up to 28 days after the last dose of IP will be summarized. In addition, for the *nab*-paclitaxel/durvalumab arm, AEs with an onset from 29 days up to 90 days after the last dose of IP will be summarized separately.

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

Treatment-emergent adverse events, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms.

Adverse events of special interest relevant to the *nab*-paclitaxel/CC-486 combination, *nab*-paclitaxel/durvalumab combination, and *nab*-paclitaxel monotherapy regimens observed in previous studies in a similar population may be identified and summarized by worst NCI CTCAE grade, 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.

10.7.2. Laboratory Assessments

Treatment group differences in each laboratory parameter with respect to the NCI CTCAE grades will be summarized by the frequency distribution of subjects with the AE grades.

All laboratory parameters will be summarized by descriptive statistics within each treatment arm, as appropriate.

10.7.3. IP Exposure

The extent of exposure to the IPs will be assessed based on the descriptive statistics on the number of cycles and IP doses administered, cumulative dose, average dose intensity, and percentage of protocol dose administered. The incidences of CC-486, *nab*-paclitaxel, and durvalumab dose reductions (although not expected for durvalumab) and dose interruptions will be summarized by treatment arm.

10.8. Study Therapy Termination

Reasons for stopping study therapy 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 IP through 28 days post last dose of the IP will be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up). In addition, deaths that occur from 29 to 90 days post last dose will be summarized in a similar manner for the *nab*-paclitaxel/durvalumab combination therapy arm.

10.10. Interim Analysis

One nonbinding interim analysis for PFS with an early stopping rule for futility will be conducted when approximately 60 events have been observed between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms. The *nab*-paclitaxel/CC-486 combination arm may be stopped early for futility if the observed HR is ≥ 1.10 given the assumed number of PFS events above, and/or if recommended by the DMC based on the safety profile of this combination regimen.

An additional interim analysis for futility with the PFS endpoint between the *nab*-paclitaxel/durvalumab combination therapy and *nab*-paclitaxel monotherapy arms will be conducted when approximately 30 PFS have been observed in the *nab*-paclitaxel/durvalumab combination arm. This is similar to approximately half of the number of events that are planned for the interim analysis between the *nab*-paclitaxel/CC-486 combination and *nab*-paclitaxel monotherapy arms mentioned above. At this time point, it is projected that approximately ≥ 60 PFS events will have been observed in the *nab*-paclitaxel monotherapy arm. The *nab*-paclitaxel/durvalumab combination therapy arm may be stopped early for futility if the observed HR is ≥ 1.10, and/or if recommended by the DMC based on the safety profile of this combination regimen. Should this occur, enrollment in the study may discontinue. The futility boundary for the interim analysis between the two arms is provided as a guidance to the DMC for their recommendations.

At the interim analysis data review on , based on the recommendation of the DMC, treatment with CC-486 was discontinued in the *nab*-paclitaxel/CC-486 combination arm; subjects in this arm may be allowed to continue on *nab*-paclitaxel single agent, at the Investigator's discretion.

Similarly, following the outcome of the interim analysis between *nab*-paclitaxel/durvalumab combination and *nab*-paclitaxel monotherapy arms, and taking into account the DMC

recommendations, subjects may be allowed to remain on either *nab*-paclitaxel or durvalumab as a single agent or both agents, at the Investigator's discretion.

10.11. Data Monitoring Committee

An independent DMC will be established with the responsibilities for safeguarding the interests of study subjects and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the coordinating Investigator and Steering Committee.

Operational details for the DMC will be detailed in the DMC charter.

10.12. Scientific Steering Committee

The conduct of this study will be overseen by a Steering Committee. The Steering Committee will serve in an advisory capacity to the Sponsor.

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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

For the purposes of this study, progressive disease (PD) of NSCLC will not require reporting as an adverse event. However, signs and symptoms (events) related to disease progression may be reported as adverse events. If reported, events of disease progression for NSCLC (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

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 as an AE. (See Section 8.8 for the definition of overdose.) Any sequela 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 sequela 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 overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for *nab*-paclitaxel, CC-486 or durvalumab 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 appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP for the monotherapy and CC-486 combination arms or to 90 days for the durvalumab combination arm, and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded on the AE page of the eCRF 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;
- 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 eCRF. 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 eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, 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 NCI CTCAE, Version 4.0

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Adverse events that are not defined in the NCI 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 IP 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 IP 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 IP caused the adverse event. 'Reasonable possibility' means

there is evidence to suggest a causal relationship between the IP 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 IP that has not been manufactured or provided by the Sponsor, 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 IP as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. 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 IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance by the Investigator.

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 eCRF. 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.

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 IP, or within 3 months of the subject's last dose of IP, are considered immediately reportable events. IP 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 female subject should be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

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 IP 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 becomes pregnant while the subject is receiving IP or within 6 months of the last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. If the male subject is receiving IP, the IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and medical monitor.

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 eCRF. 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 are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to at least 28 days after the last dose of IP for the monotherapy and CC-486 combination arms or 90 days after the last dose of IP for the durvalumab combination arm) and those made known to the Investigator at any time thereafter that are suspected of being related to IP. 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 Safety as soon as these become available. Any follow-up data will 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 Independent 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 the Sponsor 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 *nab*-paclitaxel, CC-486 or durvalumab based on the Investigator Brochures of the respective IPs.

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

For countries within the European Economic Area (EEA), the Sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP 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 the Sponsor 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.

11.7. Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of the IP and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP. Further information on risks (eg, presenting symptoms) can be found in the current version of the Investigator Brochure, including guidelines for their evaluation and treatment.

12. DISCONTINUATIONS

12.1. Study Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Adverse Event(s)
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

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.

All subjects discontinued from IP for any reason will have a treatment discontinuation visit at the time of discontinuation and should undergo treatment discontinuation procedures.

All subjects discontinued from IP will be followed for a period of 28 days after last dose of IP for the monotherapy and CC-486 combination arms or 90 days after the last dose of IP for the durvalumab combination arm for the collection of AEs.

Additionally subjects who withdraw from or discontinue treatment should be followed for progressive disease (if applicable), survival and any new anticancer therapy given.

12.2. Study Discontinuation

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

- Withdrawal of consent
- Death
- Lost to follow-up

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

- Adverse events(s)
- Protocol violation

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

Since follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and NSCLC treatment/therapy, unless the subject has specifically withdrawn consent from further follow-up. The Investigator must make every effort to obtain minimal information regarding the subject's survival status before determining that the subject is lost to follow-up.

12.3. Subject Replacement

Subjects who discontinue will not be replaced.

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 Sponsor/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 Products

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

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 the Sponsor, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (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. The Sponsor staff or its 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, study treatments, 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 ICF 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 eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by the Sponsor on public registry websites) is considered the Sponsor's confidential information. Only information that is previously disclosed by the Sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. The Sponsor's protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from the Sponsor. Information proposed for posting on the Investigator's or their institution's website must be submitted to the Sponsor for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public the Sponsor will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

14.3. Subject Information and Informed Consent

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

Documentation that informed consent occurred prior to the subject's entry into the study and of the informed consent process should be recorded in the subject's source documents including the date. The original ICF signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the subject. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's study files and a copy given to the subject. Subjects in the *nab*-paclitaxel/durvalumab arm who continue treatment beyond disease progression per RECIST 1.1 will be requested to sign a consent form at time of progression and prior to treatment continuation.

14.4. Confidentiality

The Sponsor 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). The Sponsor requires the Investigator to permit the Sponsor'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 ICF, 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 Sponsor's 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, ICF, 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.

IP can only be supplied to an Investigator by the Sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by the Sponsor 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 ICF should also be revised.

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 the Sponsor 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

The Sponsor 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 the Sponsor 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.

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 distribution of the IP 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 eCRF and entered into the clinical database per the Sponsor's 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 IP. 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 ICFs 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, Sponsor, 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;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- 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 the Sponsor 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 the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor 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. The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor 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

The Sponsor 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 Sponsor representative or designee will review the protocol, eCRFs, 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, IP storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Sponsor 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 eCRFs 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 eCRFs 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 the Sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with the Sponsor's 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, eCRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency [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 the Sponsor immediately.

17. PUBLICATIONS

As described in Section 14.2, all protocol- and amendment-related information, with the exception of the information provided by the Sponsor on public registry websites, is considered Sponsor's confidential information and is not to be used in any publications. The Sponsor protocol-related information proposed for use in a publication must be submitted to the Sponsor for review and approval, and should not be utilized in a publication without express written approval from the Sponsor, or as described in the Clinical Trial Agreement.

The Sponsor will ensure sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and 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.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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19. APPENDICES

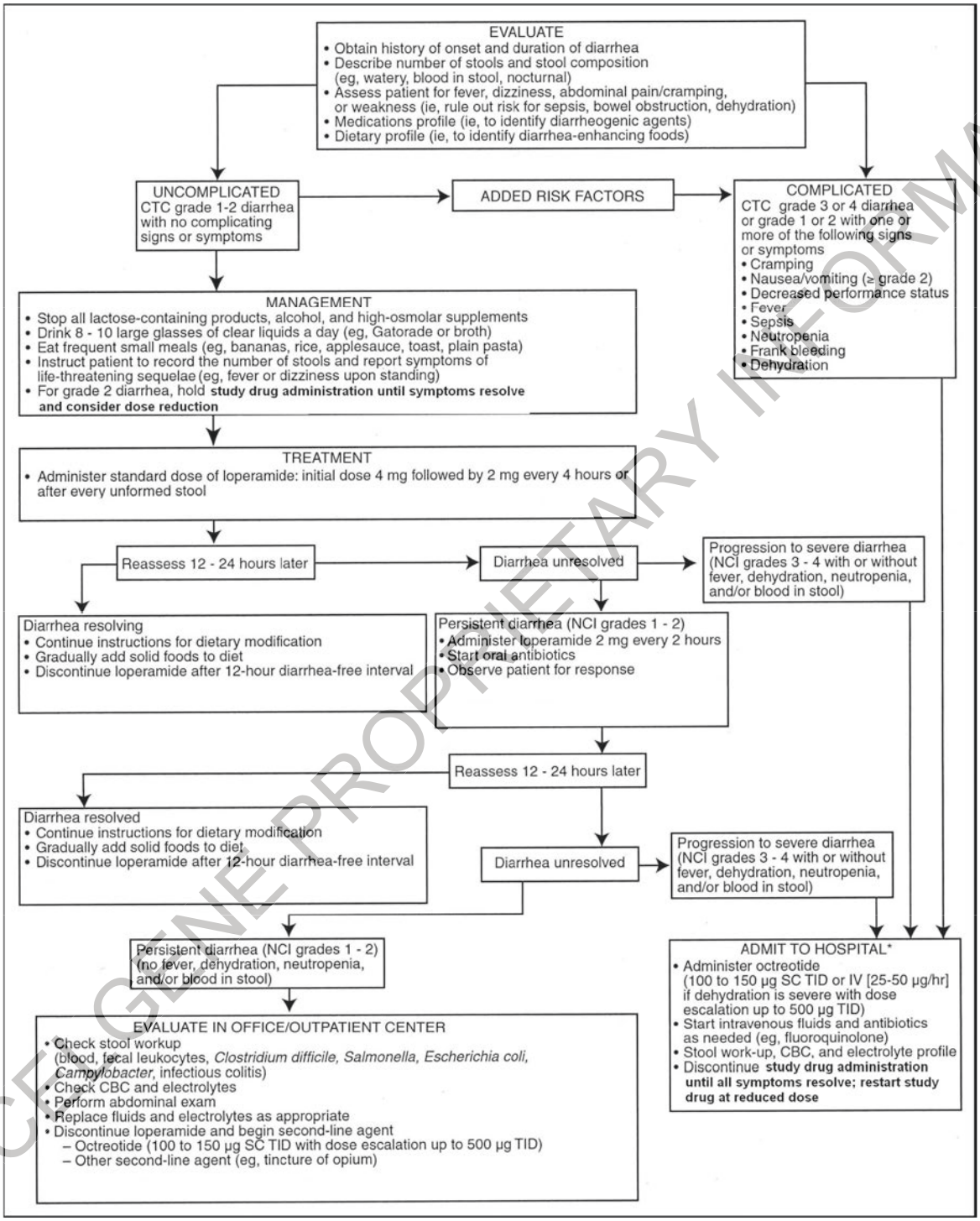
Appendix A: ECOG Performance Status Score

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: Recommendations for Management of Treatment-Induced Diarrhea

The following published guidelines (Benson, 2004) were modified in order to be consistent with the clinical study protocol.



Appendix C: Treatment Modification and Toxicity Management for *nab*-Paclitaxel /Durvalumab arm

(based on updated guidelines for Durvalumab/MEDI4736 - 09 Aug 2016 version)

General guidelines regarding treatment modification for MEDI4736 and/or *nab*-paclitaxel are provided below for immune-related AEs (Table C1), infusion-related reactions (Table C2), and non-immune-mediated reactions (Table C3).

These guidelines apply to AEs considered causally related to the durvalumab containing regimen by the reporting Investigator. Treatment modifications referring to "study regimen" would apply to both *nab*-paclitaxel and durvalumab unless AEs are not considered causally related to *nab*-paclitaxel by the reporting Investigator. In that case *nab*-paclitaxel treatment may be continued alone if deemed beneficial to the subject per Investigator's assessment.

Table C1: Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events

<table>
<tr><th>Event</th><th colspan="2">Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="4">Immune-related AEs (overall management for toxicities not noted below)</td><td colspan="2">Drug administration modifications of IP/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.
In addition to the criteria for permanent discontinuation of IP/regimen based on CTC Grade/severity (table below), permanently discontinue IP/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of IP/regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing</td><td rowspan="4">It is recommended that management of irAEs follow the guidelines presented in this table
- Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, concomitant medications, infections, etc.)
- In the absence of a clear alternative etiology, all events should be considered potentially immune related
- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone 1-2mg/kg/day PO or IV equivalent
- If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper)
- More potent immunosuppressives such as TNF inhibitors (eg, infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids
- Discontinuation of IP is not mandated for Grade 3 / 4 inflammatory reactions attributed to local tumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of IP in this situation should be based upon a benefit/risk analysis for that subject</td></tr>
<tr><td>Grade 1</td><td>No dose modification</td></tr>
<tr><td>Grade 2</td><td>Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
• IP/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper
Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with IP/study</td></tr>
</table>

Event	Dose Modifications		Toxicity Management
		regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgment, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
	Grade 3	Depending on the individual toxicity, may permanently discontinue IP/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue IP/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold IP/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume IP/regimen		

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General guidance	- Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding IP/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (radiographic changes only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (symptomatic, medical intervention indicated, limiting instrumental ADL)	• Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then the decision to reinitiate IP/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	For Grade 2 (mild to moderate new symptoms) - Monitor symptoms daily and consider hospitalization - Promptly start systemic steroids (eg, prednisone 1-2 mg/kg/day PO or IV equivalent) - Reimaging as clinically indicated - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started - If still no improvement within 3-5 days despite IV methylprednisone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[2]

[2] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Consider pulmonary and infectious disease consult - Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue IP/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the subject - Supportive Care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation) [2]
Diarrhea/ enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	- Monitor for symptoms that may be related to diarrhea/ enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea: - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	• Hold IP/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then IP/study regimen can be resumed after completion of steroid taper	For Grade 2 diarrhea: - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4mg/kg/day started. - If still no improvement within 3-5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks). **Caution**: important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab - Consult study physician if no resolution to ≤ Grade 1 in 3-4 days - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			[Category 2B recommendation])[2]
	Grade 3 or 4 Diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue IP/study regimen	For Grade 3 or 4 diarrhea: - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5mg/kg once every 2 weeks). - Caution: ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2]
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune related hepatitis**	Grade of liver function test elevation (CTCAE version 4.03) Any grade Grade 1 (AST or ALT > to 3 times ULN and/or TB > to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications)
			For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or	Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1	For Grade 2 AST or ALT and or TB elevation: - Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved.

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	TB >1.5-3.0 times ULN)	• If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then resume IP/study regimen after completion of steroid taper	- If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. - If still no improvement within 3-5 days despite 1- 2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day. - If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2]
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN: • Hold IP/study regimen dose until resolution to ≤ Grade 1 or baseline • Resume IP/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days, and after completion of steroid taper • Permanently discontinue IP/study regimen if the	For Grade 3 or 4 AST or ALT and/or TB elevation: - Promptly initiate empiric IV methylprednisolone at 1 to 4mg/kg/day or equivalent - If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		elevations do not downgrade to ≤Grade 1 or baseline within 14 days • For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue IP/study regimen • Permanently discontinue IP/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause[3]	(please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2]
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue IP/study regimen	
Nephritis or renal dysfunction (elevated serum creatinine)	Grade of elevated serum creatinine (CTCAE version 4.03) Any grade	General guidance	- Consult with nephrologist - Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)

[3] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, infections, etc.) - Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to a higher grade event
	Grade 1 [serum creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [serum creatinine>1.5-3.0X baseline; >1.5X- 3.0XULN]	Hold IP/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume IP/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. - Carefully monitor serum creatinine every 2-3 days and as clinically warranted - Consult nephrologist and consider renal biopsy if clinically indicated - If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. - Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			(please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2]. - When event returns to baseline, resume IP/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue IP/study regimen	- Carefully monitor serum creatinine on daily basis - Consult Nephrologist and consider renal biopsy if clinically indicated - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation][2]
Rash (excluding bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General guidance	• Monitor for signs and symptoms of dermatitis (rash and pruritus) • **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND IP DISCONTINUED**** ****
	Grade 1	No dose modification	For Grade 1: - Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream)

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled IP/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to Grade ≤ 1 or baseline, then resume IP/study regimen after completion of steroid taper	For Grade 2: - Obtain dermatology consult - Consider symptomatic treatment including oral antipruritics (e.g. diphenhydramine or hydroxyzine) and topical therapy (e.g. urea cream) - Consider moderate-strength topical steroid - If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent - Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	• Hold IP/study regimen until resolution to ≤ Grade 1 or baseline • If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue IP/study regimen	For Grade 3 or 4: - Consult dermatology - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Consider hospitalization - Monitor extent of rash [Rule of Nines] - Consider skin biopsy (preferably more than 1) as clinically feasible. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2] - Discuss with study physician
	Grade 4	Permanently discontinue IP/study regimen	
Endocrinopathy (eg, hyperthyroidism,	Any grade (Depending on the type of	General guidance	- Consult Endocrinologist - Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes,

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. - Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression including brain metastases, infections, etc.) - Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. - If a subject experiences an AE that is thought to be possibly of autoimmune nature (e.g. thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) - Monitor subject with appropriate endocrine function tests - If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold IP/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • IP/study regimen can be resumed once event	For Grade 2 (including those with symptomatic endocrinopathy): - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Initiate hormone replacement as needed for management - Evaluate endocrine function, and as clinically indicated, consider pituitary scan - For subjects with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (eg, 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		stabilizes and after completion of steroid taper Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with IP/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[2] - For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4 (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade/ severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold IP/study regimen dose until endocrinopathy symptom(s) are controlled • IP/study regimen can be resumed once event stabilizes and after completion of steroid taper	For Grade 3 or 4: - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Once improving, gradually taper immunosuppressive steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer related infections [Category 2B recommendation])[2] - Discuss with study physician
Immune mediated neurotoxicity (to include but not limited to limbic encephalitis. autonomic neuropathy, excluding myasthenia gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity refer to NCI CTCAE version 4.03 for defining the CTC grade/severity	General guidance	- Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.) - Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) - Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) - Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold IP/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/ neuropathic pain, consider holding IP/study regimen dose until resolution to ≤ Grade 1 - If toxicity worsens then treat as Grade 3 or Grade 4 • IP/study regimen can be resumed once event	For Grade 2: - Discuss with the study physician - Obtain Neurology Consult - Sensory neuropathy/ neuropathic pain may be managed by appropriate medications (e.g. gabapentin, duloxetine, etc.) - Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent - If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		improves to Grade ≤1 and after completion of steroid taper	
	Grade 3	• Hold IP/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue IP/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	For Grade 3 or 4: - Discuss with study physician - Obtain Neurology Consult - Consider hospitalization - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) - Once stable, gradually taper steroids over ≥ 28 days
	Grade 4	Permanently discontinue IP/study regimen	
Immune mediated peripheral neuromotor syndromes, such as Guillain-Barre and myasthenia gravis		General guidance	- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability - Subjects should be evaluated to rule out any alternative etiology (e.g. disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			- Neurophysiologic diagnostic testing (e.g. electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	For Grade 1: - Discuss with the study physician - Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above - Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	• Hold IP/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue IP/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For Grade 2: - Discuss with the study physician - Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above - Obtain a Neurology Consult - Sensory neuropathy/ neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. o If Myasthenia Gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	• Hold IP/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue IP/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: - Discuss with study physician - Recommend hospitalization - Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.
	Grade 4	Permanently discontinue IP/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			o If Myasthenia Gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: ◦ Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

AChE = acetylcholine esterase; ADL = activities of daily living; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CT = computed tomography; CTC = Common Terminology Criteria; FT4 = free thyroxine; GI = gastrointestinal; ILD = interstitial lung disease; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PCP = pneumocystis pneumonia; PO = oral; TB = total bilirubin; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Table C2: Treatment Modification and Toxicity Management Guidelines for Infusion-related Adverse Events

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any grade	General guidance	- Management per institutional standard at the discretion of investigator - Monitor subjects for signs and symptoms of infusion-related reactions (e.g. fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of IP/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: - Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator - Consider premedication per institutional standard prior to subsequent doses - Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
Grade 2	The infusion rate of IP/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3 or 4	Permanently discontinue IP/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g. IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

IM = intramuscular; IV = intravenous.

Table C3: Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
Grade 1	No dose adjustment	Treat accordingly as per institutional standard
Grade 2	Hold IP/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
Grade 3	Hold IP/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration. Otherwise, discontinue IP/study regimen	Treat accordingly as per institutional standard
Grade 4	Discontinue IP/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

AE = adverse event; CTC = Common Terminology Criteria.

Celgene Signing Page

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