Protocol Title: A Phase 2 Multicenter, Randomized, Placebo Controlled, Double-Blind Study To Assess The Safety And Efficacy Of CC-486 (Oral Azacitidine) In Combination With Pembrolizumab (Mk-3475) Versus Pembrolizumab Plus Placebo In Subjects With Previously Treated Locally Advanced Or Metastatic Non-Small Cell Lung Cancer

NCT Number: NCT02546986

Protocol Amendment 1 Date: 14 December 2015

DISCLOSURE

REDACTED PROTOCOL AMENDMENT 1

CC-486-NSCL-001

A PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF CC-486 (ORAL AZACITIDINE) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) VERSUS PEMBROLIZUMAB PLUS PLACEBO IN SUBJECTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

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A PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF CC-486 (ORAL AZACITIDINE) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) VERSUS PEMBROLIZUMAB PLUS PLACEBO IN SUBJECTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

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PROTOCOL SUMMARY

Study Title

A Phase 2 multicenter, randomized, placebo controlled, double-blind study to assess the safety and efficacy of CC-486 (oral azacitidine) in combination with pembrolizumab (MK-3475) versus pembrolizumab plus placebo in subjects with previously treated locally advanced or metastatic non-small cell lung cancer

Indication

Second-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

Objectives

Primary Objective:

- To estimate the efficacy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo based on progression-free survival (PFS) as measured using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria

Secondary Objectives:

- To estimate disease control rate (DCR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate overall survival (OS) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate overall response rate (ORR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate safety and tolerability of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate the impact of pembrolizumab on the pharmacokinetics of CC-486

Exploratory Objectives:

- To determine the preliminary efficacy (immune-related [ir] PFS, irDCR, irORR) of CC-486 in combination with pembrolizumab versus pembrolizumab plus placebo based on irRECIST criteria
- To explore mechanism and biomarkers associated with efficacy of CC-486 in combination with pembrolizumab versus pembrolizumab plus placebo,

Study Design

This is a Phase 2, multicenter, international, randomized, placebo controlled double-blind study to assess the safety and efficacy of the combination therapy of CC-486 plus pembrolizumab versus placebo plus pembrolizumab in previously treated subjects with locally advanced or metastatic NSCLC who have received only one prior platinum-based chemotherapy regimen.

Approximately 90 subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or placebo plus pembrolizumab. A safety analysis will be performed in the first 10 subjects in each arm after the completion of at least 1 cycle of treatment.

The randomization will be stratified by histology (non-squamous versus squamous).

An independent Data Monitoring Committee (iDMC) will be established to evaluate safety. Following the initial iDMC data review meeting, the iDMC will meet approximately every 6 months per DMC charter (or more often if requested by the DMC Chairman) to assess safety data. Details are outlined in the DMC charter.

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

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Adult subjects with histologically confirmed diagnosis of locally advanced or metastatic NSCLC, lacking or with unknown anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) mutations, who have been treated with only 1 prior platinum-based chemotherapy regimen for locally advanced or metastatic disease.

Length of Study

Enrollment is expected to take approximately 12 months to complete. The total length of this Phase 2 study with follow-up is estimated to be approximately 2 years. The primary analysis will be conducted when 70 PFS events have occurred.

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 pre-specified in the protocol, whichever is the later date.

Study Treatments

CC-486/placebo will be administered at a dose of 300 mg orally daily on days 1-14 of a 21-day cycle. Pembrolizumab will be administered as a 30-minute intravenous (IV) infusion at a dose of 200 mg (4 x 50 mg vials) on day 1 of a 21-day cycle.

Subjects may remain on treatment until radiologic disease progression (for exceptions refer to Section 6.4.3), unacceptable toxicity, initiation of a new anticancer therapy, withdrawal of consent, subject refusal, physician decision, or death.

Overview of Efficacy Assessments

All subjects will be evaluated for tumor response and progression by Investigator assessment according to RECIST 1.1 guidelines at screening and every 6 weeks (± 5 days) from randomization for the first 24 weeks, and every 9 weeks thereafter until documented disease progression (for exceptions refer to Section 6.4.3), start of new anticancer therapy, or withdrawal of consent. Subjects will also be evaluated according to irRECIST guidelines in cases of progressive disease (PD) per RECIST 1.1.

Response assessments will include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, upper abdomen, including whole liver and kidney and, if clinically indicated, pelvis. Pelvis scan should be performed only with MRI unless CT is local standard of care at the site. Bone scans will only be performed at baseline if clinically indicated. If the baseline bone scan is suggestive of metastasis, a CT or MRI should be performed and further follow-up of these lesions will follow the protocol schedule. Bone scans during the trial will only be performed if clinically indicated. If suggestive of new lesions, a CT or MRI will be performed to confirm progression.

In the follow-up phase, anticancer treatment administered following the last dose of investigational product [(IP), also referred to as investigational medicinal product (IMP)] and survival will be followed every 8 weeks (± 5 days) until death, withdrawal of consent, or lost-to-follow-up, whichever occurs first, or the End of Trial.

Overview of Safety Assessments

All subjects will be monitored for adverse events, starting from the time the subject signs the informed consent form (ICF) until 30 days after the last dose of either study drug. A thorough evaluation of medical conditions will be conducted during screening for eligibility. Documented physical examination (PE), vital signs, laboratory assessments, (eg, serum chemistry, hematology), 12-lead electrocardiogram (ECG), urinalysis, and Eastern Cooperative Oncology Group (ECOG) performance status will be monitored regularly. Preventative measures will be taken to avoid pregnancy in study subjects or their partners, and females of child-bearing potential will have regular pregnancy testing performed. The full schedule of assessments is described in Table 2 and Section 6.

Overview of Statistical Methods

This is a double-blind, placebo-controlled, randomized, phase 2 trial designed to evaluate the efficacy and safety/tolerability of CC-486 plus pembrolizumab versus pembrolizumab plus placebo, in subjects with previously treated locally advanced or metastatic non-small cell lung cancer. The primary endpoint is PFS based on Investigator review.

Sample Size

The primary goal of this study is to provide estimates of the difference in efficacy and safety between CC-486 + pembrolizumab and placebo + pembrolizumab. Approximately 90 subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or placebo plus pembrolizumab. Primary analysis will be conducted when 70 PFS events occur. In this particular setting, a formal power calculation was not conducted.

Efficacy Analysis

Efficacy analyses will be performed using the intent-to-treat (ITT) population.

The median PFS in each stratum and treatment arm will be calculated based on Kaplan-Meier estimates along with corresponding two-sided 90% confidence interval (CI). In addition, the Cox proportional hazards regression model with treatment and any stratification factors will be performed to obtain the point estimate of hazard ratio (HR) and two-sided 90% CI.

The secondary efficacy endpoint of OS will be analyzed similarly to PFS. Other secondary endpoints of overall response rate (ORR), and disease control rate (DCR) will be evaluated as

well. A two-sided 90% CI of the difference in ORR and DCR between the two treatment arms will be provided.

Safety Analysis

Safety analysis will be performed using the safety population. Safety and tolerability will be monitored through continuous reporting of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, and incidence of subjects experiencing adverse events resulting in dose reductions, dose interruptions, and/or premature discontinuation of study drugs. Treatment-emergent adverse events (TEAEs), TEAEs leading to death or discontinuation from treatment, events assessed as Grade 3 or Grade 4, vital signs, weight, clinical laboratory information, and concomitant medications/procedures will be tabulated and summarized.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All TEAEs will be summarized by system organ class and preferred term, frequency, severity grade based on the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) and relationship to treatment. Serious TEAEs, TEAEs of interest, and TEAEs leading to discontinuation, dose reduction, or interruption, or death will be summarized/ listed separately.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Disease Background

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in both men and women. Globally, approximately 1,825,000 new cases of lung cancer were diagnosed in 2012, and 1,590,000 deaths occurred due to this disease (Globocan, 2012). The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases and includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer seen in the United States (US) and is also the most frequently occurring cell type in nonsmokers (Speicher, 2000).

Cigarette smoking remains the most important risk factor for lung cancer, although approximately 15% of all lung cancers are diagnosed in patients who never smoked.

One reason for the high mortality rate of lung cancer is the advanced stage at diagnosis; only 25-30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery (Fossella, 2000; Lang-Lazdunski, 2013). The majority of patients are diagnosed with locally advanced or metastatic disease and are not candidates for surgery.

1.2. Treatment Options in Second-line Metastatic NSCLC

In patients with metastatic NSCLC who have experienced disease progression either during or after first-line therapy and have an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2, single agent docetaxel, gemcitabine, or erlotinib is recommended if not previously given. Pemetrexed is another option for the non-squamous subtype of NSCLC (NCCN, 2014, ESMO, 2014).

Docetaxel was shown to be superior to best supportive care (BSC), vinorelbine and ifosfamide; nevertheless, using either the weekly or three-weekly schedule in multiple randomized studies the observed response rate with docetaxel ranged from 3% to 12%, progression-free survival (PFS) from 1.9 to 3.4 months, and overall survival (OS) from 5.4 to 9.2 months (Shepherd, 2000; Fossella, 2000; Bria, 2006).

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, 2014). 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 PFS (4.5 vs 3.0 months; HR, 0.762; P < .0001) (Perol, 2014).

Gemcitabine showed modest activity in a phase II study with a 6.2% partial response and 17 weeks median duration of survival in advanced NSCLC subjects who progressed on first-line cisplatin-containing therapy (Sculier, 2000). Another phase II study found a partial response in 19% of subjects treated with gemcitabine as a second-line agent, and a median duration of response of 29 weeks (Crino, 1999). In a third trial evaluating gemcitabine plus BSC versus BSC alone, tumor response was seen in 19% of gemcitabine-treated subjects while response was not measured in subjects treated with BSC alone (Anderson, 2000). There was no difference in OS (5.7 versus 5.9 months, respectively). The difference in the results between the trials may be due to the percentage of stage III versus stage IV subjects included in the trials. In the study by Sculier et al. 96% of subjects had stage IV disease compared to 59% and 40% in Crino et al. and Anderson et al., respectively.

Erlotinib has been proven to be superior to BSC with significantly improved survival (6.7 vs. 4.7 months), PFS (2.2 vs. 1.8 months), and delayed time to symptom deterioration (Shepherd, 2005).

Gefitinib is approved in the EU for the treatment of advanced and metastatic NSCLC with activating mutations of epidermal growth factor receptor (EGFR) only. Although a higher response rate was in favor of gefitinib compared to placebo (8% vs. 1%), median time to progression (TTP) (3.0 vs. 2.6 months) and survival (5.6 vs. 5.1 months) were similar in the 2 groups (Thatcher, 2005). A non-inferiority trial compared gefitinib to docetaxel in NSCLC patients after 1 or 2 lines of chemotherapy (Kim, 2008). A similar median survival (7.6 vs. 8 months) and TTP (2.2 vs. 2.7 months) were observed, but less toxicity and better quality of life favored the gefitinib arm.

Pemetrexed showed clinically equivalent efficacy outcomes but better tolerability when compared to docetaxel in patients with the non-squamous subtype of NSCLC (Hanna, 2004; Peterson, 2007).

An overview of the published data with the above described agents are summarized in Table 1.

Table 1: Main Data in Pretreated NSCLC Subjects

Compound	Line of treatment	Histology	N	RR (%)	Median TTP/PFS (months)	OS (months)
Docetaxel	2nd	All	2557	2.7-12.6	1.9-3.4	5.4-9.2
Gemcitabine	2nd	All	65	6.2[1]	--	4.2[2]
Erlotinib	2nd 3rd	All	806	6.2-9	1.7-2.2	6.7-9.2
Gefitinib	2nd 3rd	All	1862	8.0-9.1	2.2-3.0	5.6-7.6
Pemetrexed	2nd	All[3]	871	4.3-9.1	2.6-2.9	6.7-8.3

[1] This value represents partial response.
[2] This value represents median duration of survival.
[3] A retrospective analysis found that pemetrexed only showed significantly higher survival when compared to docetaxel in the non-squamous subgroup. Docetaxel had statistically better survival in the squamous cell subgroup

Personalized treatment based on molecular characteristics of the tumor has also become the standard of care. In addition to the above guidelines, patients whose tumors are positive for the EGFR and/or anaplastic lymphoma kinase (ALK) mutation(s) should receive targeted therapy. The EGFR mutation which results in the activation of the EGFR tyrosine kinase domain has been reported in about 20-25% of non-squamous NSCLC cases and less than 5% in tumors with squamous histology. Erlotinib and afatinib are EGFR tyrosine kinase inhibitors (TKIs) indicated for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, the most commonly found mutations in NSCLC (Tarceva® Package Insert; Gilotrif® Package Insert; NCCN, 2014). Patients who progress after first-line therapy are still recommended to be continued on erlotinib or afatinib as part of second-line therapy (NCCN, 2014). Anaplastic lymphoma kinase translocation, another key driver mutation, occurs in roughly 5% of NSCLC cases (Shaw, 2013), and it is mostly associated with the adenocarcinoma subtype (Bang, 2011; Xalkori Package Insert). Tumors with this mutation are amenable to treatment with crizotinib, an ALK, MET, and ROS1 tyrosine kinase inhibitor, and thus, crizotinib is used in first-line therapy for metastatic ALK-positive NSCLC patients. For patients who progress after first-line therapy, crizotinib or the recently approved ALK inhibitor, ceritinib, is recommended as part of second-line therapy (NCCN, 2014). This trial will focus on second-line therapy for subjects who do not possess these 2 driver mutations. Thus, EGFR-positive and ALK-positive subjects will be excluded from this trial.

The reported response rate to second-line therapy has generally been less than 10% (NCCN, 2014), and many patients who respond to second-line therapy eventually develop resistance. The limited effective second-line therapy options available call for the investigation of novel approaches to drug therapy in advanced NSCLC.

1.3. Overview of CC-486

CC-486 is an orally bioavailable formulation of azacitidine (AZA). Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism, and causes cytotoxicity.

Vidaza® (azacitidine injection) is approved by the US Food and Drug Administration (FDA) for five subtypes of the French American British (FAB) classification system of myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMMoL). Vidaza is also approved by the European Commission for the treatment of adult MDS, acute myeloid leukemia (AML) and CMMoL patients who are not eligible for hematopoietic stem cell transplantation. Vidaza can be administered by intravenous (IV) or subcutaneous (SC) routes as designated by country approval.

After its incorporation into a cell's DNA during the S-phase of the cell cycle, AZA 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 suppresion of genes (Miranda, 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 gene silencing can thus contribute to the establishment and maintenance of the transformed state and limit the effectiveness of anticancer therapies.

CC-486 entered clinical testing in 2006 in subjects with MDS, CMMoL, and AML. The AZA PH US 2007 CL 005 study has shown that CC-486 is bioavailable and a maximum tolerated dose (MTD) of 480 mg daily for 7 days of a 28-day cycle was defined based on dose-limiting diarrhea at the 600 mg dose (Garcia-Manero, 2011). As expected, reversible and manageable myelosuppression was observed. Pharmacodynamic activity (DNA hypomethylation) and clinical responses were observed with CC-486, although the cross-over design (with SC Vidaza administered during Cycle 1) confounded the interpretation of these responses in Part 1 of the study.

The second part of the AZA PH US 2007 CL 005 study explored both daily and twice daily extended dosing schedules of 14 and 21 days out of 28 days in a non-crossover design. CC-486 administered at 300 mg once daily (QD) for 14 or 21 days of a 28-day cycle produces cumulative exposures (area under the concentration-time curve [AUC] per cycle) that are approximately 40% and 60% of the exposure achieved with the labeled dose and schedule of Vidaza, respectively. Daily doses of 300 mg have proven to be tolerated on both the 14 and 21 out of 28-day schedules with myelosuppression, gastrointestinal (GI) symptoms, and fatigue being the most common toxicities (Garcia-Manero, 2011).

In the AZA PH US 2007 CL 005 study, DNA methylation levels in blood were measured as a pharmacodynamic (PD) endpoint, to determine DNA hypomethylating activity of CC-486. In summary, it was confirmed that CC-486 is biologically active, reducing DNA methylation when administered at low doses on extended schedules.

CC-486 is also under clinical investigation, either as monotherapy or in combination with other investigational products, for the treatment of lymphoma, multiple myeloma, and relapsed or refractory solid tumors (eg, urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra; pancreatic carcinoma; breast cancer; ovarian cancer; nasopharyngeal carcinoma; cervical carcinoma; anal carcinoma; and merkel cell carcinoma).

There are 2 ongoing studies evaluating PK of CC-486 (AZA-ST-001 and CC-223-NSCL-001). Part 1 of the AZA-ST-001 study assessed the impact (if any) of carboplatin or ABI-007 on the PK of CC-486 and the impact (if any) of CC-486 on the PK of carboplatin or ABI-007. Preliminary results showed that in subjects from Arms A and B, following administration of CC-486 alone or in combination with carboplatin or ABI-007, azacitidine was rapidly absorbed and reached T_{max} within approximately 1.0 hour post-dose (median); azacitidine PK parameters (AUC, C_{max}, $t_{1/2}$, CL/F, and Vz/F) were comparable following administration of CC-486 alone or in combination. Similarly, carboplatin and ABI-007 PK parameters were similar following administration of carboplatin or ABI-007 alone or in combination with CC-486. In subjects from the 3 arms (Arms A, B, and C, i.e., CC-486 monotherapy), global genomic hypomethylation was observed in PBMCs, with maximum

effect on Day 15. A PK/PD (AUC/hypomethylation change on Day 15) correlation was noted ($r > 0.5$; $p < 0.01$).

1.3.1. CC-486 Experience in Solid Tumors

A Phase 1 study of CC-486 in combination with carboplatin or *nab*-paclitaxel, or as a single agent in subjects with relapsed or refractory solid tumors (AZA-ST-001) was initiated on 30 Nov 2011. In Part 1 of this two-part study, CC-486 at escalating doses of 200 or 300 mg was administered on Days 1 to 14 of a 21-day cycle in three separate arms of the study (Arm A, Arm B, Arm C).

In Arm A of AZA-ST-001, subjects received carboplatin (AUC = 4) on Day 8 of each cycle and in Arm B, subjects received *nab*-paclitaxel 100 mg/m^2 beginning on Day 8. For Arm A, both 200 mg and 300 mg CC-486 were well tolerated with carboplatin AUC = 4. For Arm B, initially, *nab*-paclitaxel was administered weekly starting on Cycle 1 Day 8 but dose-limiting neutropenia was encountered on this schedule at the first dose level of CC-486. The protocol was amended to administer *nab*-paclitaxel on Days 8 and 15 of each cycle (ie, 2 out of 3 weeks) and this was well tolerated in combination with CC-486 at 200 mg. When the CC-486 dose was escalated to 300 mg, dose-limiting neutropenia was again encountered, making the 200 mg the MTD of CC-486 in combination with *nab*-paclitaxel 100 mg/m^2 on a 2- out of 3-week schedule. Arm C of study AZA-ST-001 assessed the safety of continuous administration of CC-486 on a 21- out of 21-day schedule. This schedule proved not to be tolerable, with profound granulocytopenia manifesting in 2 out of 6 subjects at the 300 mg dose level during Cycle 2. Single agent CC-486 was better tolerated in subjects when used at the dose of 300 mg daily for 2- out of 3-week cycle with a manageable safety profile, and the recommended Phase 2 dose for Arm C was determined to be 300 mg on Days 1 to 14 of each 21-day cycle.

The most promising hints of activity in AZA-ST-001 were observed in Arm B. Of 8 evaluable subjects with relapsed pancreatic carcinoma, 1 had a partial response (PR) and 3 others had stable disease (SD) > 16 weeks for a disease control rate (DCR) of 50%. CC-486 has also shown promising efficacy in subjects with relapsed or refractory NSCLC (N = 20). Although the efficacy data are not yet fully mature, objective responses were observed, including 2 PRs in NSCLC subjects. An additional 8 subjects with NSCLC had stable disease for periods ranging from 4 to 9 months. Furthermore, dramatic objective responses were observed in subjects with relapsed cervical and endometrial cancer. These observations, although promising, do not provide conclusive evidence of an epigenetic modifying effect by CC-486.

Please refer to the Azacitidine IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the azacitidine/CC-486.

1.4. Overview of Pembrolizumab

The programmed cell death protein-1 (PD-1) is an immune-checkpoint receptor expressed by T cells upon activation. The normal function of PD-1 upon binding by its ligands, programmed death-ligand 1 (PD-L1) and PD-L2, is to moderate ongoing immune responses and prevent autoimmunity (Harvey, 2014). Some tumor cells up-regulate the PD-1 ligands to evade active T-cell immune surveillance. Pembrolizumab is a highly selective humanized monoclonal antibody (mAb) that binds to the PD-1 receptor and directly blocks the interaction between PD-1 and its ligands, thereby enhancing tumor regression and ultimately immune rejection (pembrolizumab IB). Pembrolizumab is being investigated in various oncology indications including melanoma, NSCLC, renal cell carcinoma (RCC), breast cancer, multiple myeloma (MM), microsatellite unstable tumors, and head and neck cancer. Pembrolizumab [Keytruda (US)], is approved for treatment of melanoma in several countries; in the US it is indicated for the treatment of advanced, unresectable or metastatic malignant melanoma in patients with disease progression after prior treatment with ipilimumab and, for BRAF V600 mutation-positive patients, a BRAF inhibitor, while in the EU it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been granted approval in the US for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, and who have disease progression on or after platinum-containing chemotherapy.

1.4.1. Pembrolizumab Experience in Solid Tumors and Safety

An open-label phase 1 trial (Keynote 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks, in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. Based on PK data showing a half-life of 21 days, the dosing frequency in the expansion cohort has been changed to every 3 weeks.

The choice of the 200 mg every 3 weeks as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

The ongoing expansion cohort in Keynote 001 is enrolling subjects with NSCLC.

Keynote 001, Part C enrolled 495 subjects with NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) to receive monotherapy pembrolizumab. The ORR was 19.4% (18.0% in the 394 previously treated subjects and 24.8% in the 101 previously untreated subjects). The median PFS was 3.7 months, and the median OS was 12.0 months (Garon, 2015).

Pembrolizumab has been generally well-tolerated. The most common treatment related adverse events were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related adverse events of an inflammatory or immune-mediated nature that occurred in more than 2% of

patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy. Pneumonitis of grade 3 or greater was observed in 9 patients (1.8%), including 1 (0.2%) who died. At the time of this analysis, 2 cases of pneumonitis (both grade 1 or 2) were ongoing (Garon, 2015).

Please refer to the pembrolizumab IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile.

1.5. Study Rationale

Both CC-486 and pembrolizumab have shown promising activity and acceptable tolerability in patients with relapsed or refractory NSCLC as detailed in Sections 1.3.1 and 1.4.1.

The reported response rate to second-line therapy in NSCLC has generally been less than 10% (NCCN, 2014), and many patients who do respond eventually develop resistance. The limited availability of effective second-line therapy options call for the investigation of novel approaches to drug therapy in advanced NSCLC. One potential strategy is the use of epigenetic agents, such as CC-486, to prime the tumor to become more responsive to immunotherapy. This approach is proposed by combining CC-486 with pembrolizumab in this trial.

Studies have shown that epigenetic events such as hypermethylation of the promoter sites on certain genes may play a role in tumor progression in lung cancer (Topaloglu, 2004). Importantly, unlike gene mutations, DNA methylation is reversible and can be inhibited by a DNMTi (Zeng, 2013). There are currently 4 drugs targeting epigenetic changes that have been approved by the FDA for use in hematologic malignancies, i.e., 2 DNMT inhibitors for myelodysplastic syndrome (azacitidine and decitabine) and 2 histone deacetylase (HDAC) inhibitors for cutaneous T-cell lymphoma (vorinostat and romidepsin). A recent study using the combination epigenetic therapy of azacitidine and entinostat, an HDAC inhibitor, in subjects with recurrent metastatic NSCLC who had extensive prior systemic therapy yielded some interesting results (Juergens, 2011). Though only two of the 65 subjects had robust and durable RECIST criteria responses to this therapy, a group of these subjects were observed during follow-up to have responded to various subsequent therapeutic regimens (Juergens, 2011). Five of these subjects received 1 of 2 investigational immunotherapy drugs, anti-PD1 or anti-PD-L1 antibody. Preliminary data revealed that 3 subjects experienced durable partial responses for over a year while the other two subjects had stable disease on therapy for more than 6 months (Brahmer, 2013).

Previous PD-1 immune-checkpoint targeting monotherapy studies in subjects with advanced NSCLC who received previous systemic therapy reported only a 16 to 17% response rate (Brahmer, 2012; Topalian, 2012, Brahmer, 2013 abstract, Garon 2014).

The results of the above study led to the hypothesis that azacitidine may prime the tumor to become more responsive to immunotherapy. There are several possible mechanisms as to how this may occur (Brahmer 2013):

- Azacitidine induces the type I IFN pathway and subsequently upregulates suppressed antigen-presenting molecules, enhancing intratumoral inflammatory response.

- Azacitidine reactivates the production of tumor antigens, such as cancer testes antigens, that are found in lung cancer.
- Azacitidine activates silenced effector cytokine genes in anergized T cells.

Further support for using CC-486 in combination with pembrolizumab is the fact that epigenetic treatment of NSCLC cell lines has been found to increase expression of PD-1 and PD-L1. Co-administration of a PD-1 pathway inhibitor would shift the balance in favor of the immune-enhancing effects of epigenetic modulators on T cells (Brahmer, 2013). Thus, the combination of azacitidine and a PD-1 pathway inhibitor would mechanistically complement each other for the purpose of cancer treatment.

Current treatment options for metastatic NSCLC patients who have progressed on first-line therapy are limited. The use of epigenetic modifying agents such as CC-486 to overcome immune resistance mechanisms of tumors is an interesting strategy. Here we propose to evaluate the ability of CC-486 to sensitize tumor cells to PD-1 inhibition with pembrolizumab.

To explore the hypothesized mechanism of CC-486 priming to pembrolizumab efficacy, and potentially identify biomarkers to predict patients that would benefit from this therapeutic regimen, tissue samples will be collected from patients pre-therapy and during therapy for cellular and molecular analyses. Submission of archival or fresh tumor tissue pre-therapy is mandatory. Blood, serum and saliva will also be collected.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To estimate the efficacy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo based on PFS as measured using RECIST 1.1 criteria

2.2. Secondary Objectives

The secondary objectives of the study are:

- To estimate DCR of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate OS of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate ORR of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate safety and tolerability of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate the impact of pembrolizumab on the pharmacokinetics of CC-486

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine the preliminary efficacy (immune-related [ir] PFS, irDCR, irORR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo based on irRECIST criteria
- To explore mechanism and biomarkers associated with efficacy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo,

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- PFS measured as time from randomization to progression according to RECIST 1.1 (based on Investigator assessment)

3.2. Secondary Endpoints

- Number (%) of subjects with SD for ≥ 18 weeks, complete response (CR) or PR (DCR).
- Overall survival.
- Number (%) of subjects who achieve an objective CR or PR (ORR).
- Safety to include the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, Grade 3-4 TEAEs, TEAEs of special interest, and laboratory abnormalities and other safety parameters.
- Plasma PK parameters such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance (CL/F) and apparent volume of distribution (Vz/F) for CC-486.

3.3. Exploratory Endpoint(s)

- Exploratory efficacy as measured by irPFS, irDCR, and irORR based on Investigator assessment using irRECIST.
-
-
- DNA analyses, gene expression and soluble factors in blood.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, multicenter, international, randomized, placebo controlled, double-blind study to assess the safety and efficacy of CC-486 and pembrolizumab combination therapy versus pembrolizumab plus placebo in previously treated subjects with locally advanced or metastatic NSCLC who have received only one prior platinum-based chemotherapy regimen.

Approximately 90 subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or placebo plus pembrolizumab as follows:

- Arm A: CC-486 300 mg administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle
- Arm B: Placebo administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle

A safety analysis will be performed in the first 10 subjects in each arm after the last enrolled subject has completed 1 cycle of treatment.

Randomization will be stratified between treatment arms by:

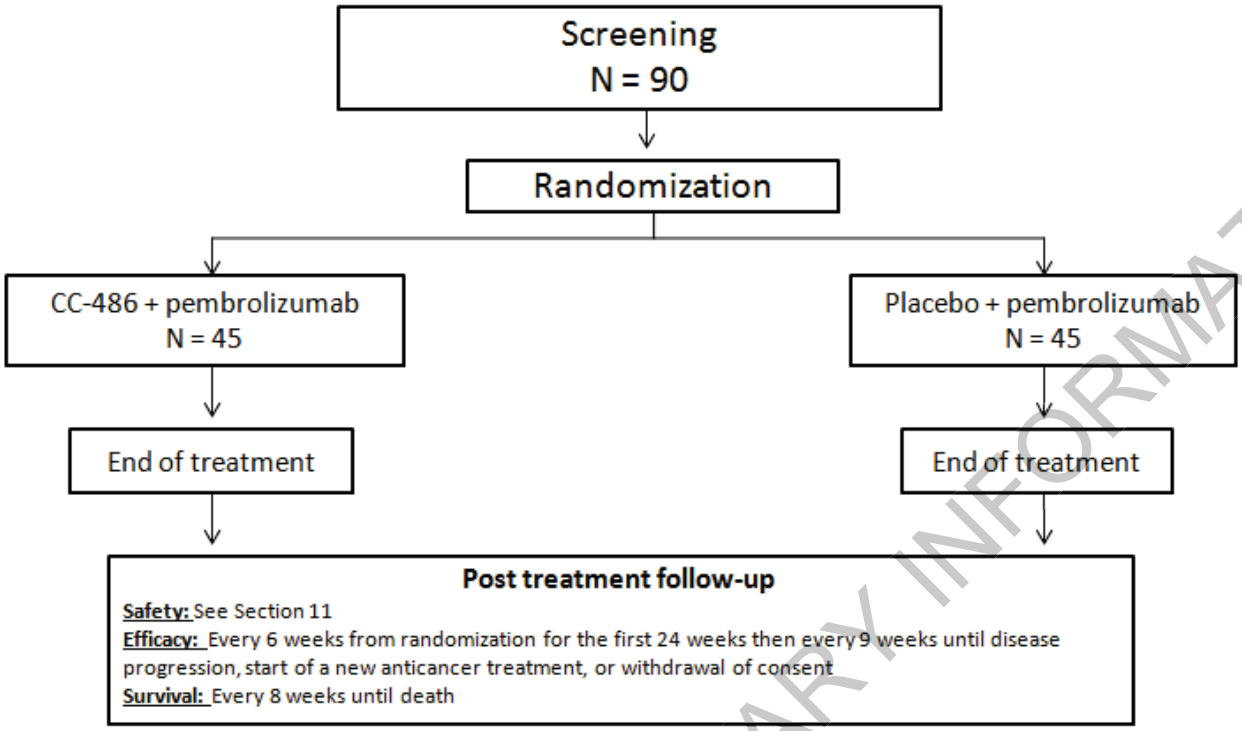
- Histology (non-squamous versus squamous)

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

The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Primary analysis will be conducted when 70 PFS events have occurred.

Figure 1: Overall Study Design



4.2. Study Duration

Enrollment is expected to take approximately 12 months to complete. Completion of active treatment and post-treatment follow-up is expected to take an additional 12 months. The entire study is expected to last approximately 2 years.

4.3. 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 the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

5. TABLE OF EVENTS

Table 2: Table of Events

Events	Screening Period	Treatment Period[a]						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-28 to -1	1[b]	14	1	14	1	EOT	Disease Progression/ Survival
Informed consent	X							
Demographics	X							
Prior cancer history	X							
Prior cancer therapies[c]	X							
Complete medical history	X							
Prior/ concomitant medication evaluation[d]	X (≤ 28d from screening)	Continuous, until 28 days after last dose						
Prior/ concomitant procedures evaluation[e]	X (≤ 28d from screening)	Continuous, until 28 days after last dose						
Inclusion/exclusion criteria	X							
IRT registration	X							
IRT randomization		X[f]						
Adverse event evaluation	Continuous after informed consent signature, until 30 days after discontinuation of either drug. See Section 11 for additional details on AE reporting timeframe							
Physical examination (source documented only)	X	X		X		X	X	

Table 2: Table of Events (Continued)

Events	Screening Period	Treatment Period[a]						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-28 to -1	1[b]	14	1	14	1	EOT	Disease Progression/ Survival
Weight	X	X		X		X	X	
Height	X							
Vital signs	X	X		X		X	X	
ECOG performance status	X	X		X		X	X	
Hematology laboratory[g]	X	X	X	X	X	X	X	
Coagulation[h]	X							
HBV and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb)	X						X	
Chemistry laboratory[i]	X	X	X	X	X	X	X	
Lipid panel[j]	X					Every 4th cycle	X	
Thyroid test	X					X Cycle 3 Day 1 then every 6 weeks		
Urinalysis[k]	X	X		X		X	X	
12-lead electrocardiogram	X						X	

Table 2: Table of Events (Continued)

Events	Screening Period	Treatment Period[a]						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-28 to -1	1[b]	14	1	14	1	EOT	Disease Progression/ Survival
Serum β-hCG (for all FCBP)[l]	X							
Serum or Urine β-hCG (for all FCBP)[l]	X (w/in72 hours)	X		X		X	X	
PK blood draws sampling (See Section 6.5 for timepoints)		X		X				
Tumor biopsy for Biomarker Analyses	X (Mandatory – archival or fresh tumor collection)				X (Optional)			
Blood for Biomarker DNA Analyses		X		X				
Blood for Biomarker RNA Analyses		X		X			X	
Serum for Biomarker Analyses		X		X		X[m]	X	
Saliva for Germline DNA Analysis		X						

Table 2: Table of Events (Continued)

Events	Screening Period	Treatment Period[a]						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-28 to -1	1[b]	14	1	14	1	EOT	Disease Progression/ Survival
Tumor evaluation (CT/MRI)	X	RECIST 1.1 algorithm: Every 6 weeks (± 5 days) from randomization for the first 24 weeks then every 9 weeks until disease progression (for exceptions refer to Section 6.4.3) or start of a new anticancer treatment, or withdrawal of consent The irRECIST will be evaluated as exploratory efficacy assessment. For additional details, see Sections 6.4.2 , 6.4.3 and Appendix B, Section 19.1						
Bone Scan	Only if clinically indicated							
CT Scan of the Head or Brain MRI	X	Only if clinically indicated						
Administer CC-486/placebo		Daily on Days 1-14						
Administer pembrolizumab		X^n		X		On Day 1 only		
IP accountability		X		X		X	X	
Survival follow-up								Every 8 weeks (+/- 5 days)
Anticancer therapy since IP discontinuation								At every survival follow-up visit

Abbreviations: β-hCG = beta human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FCBP = females of child bearing potential; IP = investigational product; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; IRT = interactive response technology; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors

[a] All visits have a ± 2-day window, except Cycle 1 Day 1 which must occur within 28 days from Informed Consent Form signature, and survival follow-up which has a ±5-day window.

[b] Cycle 1 Day 1 evaluations can be omitted if Screening evaluations are performed within 72 hours of Cycle 1 Day 1.
[c] Prior cancer therapies include surgery, radiation, systemic or any other therapy (eg, hormonal, locoregional) for the subject's cancer
[d] Prior/concomitant medication evaluation ≤ 28 days before screening through 28 days after last dose.
[e] Prior/concomitant procedures evaluation ≤ 28 days before screening through 28 days after last dose.
[f] Prior to receiving first dose.
[g] Hematology includes complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count. ANC should be measured with automated count where available.
[h] Coagulation tests, including prothrombin time (PT), partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT) and international normalized ration (INR)
[I] Chemistry includes (but is not limited to) sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, fasting glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase, total bilirubin (indirect and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
[j] Lipid Panel parameters include total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
[k] Urinalysis (a urine dipstick may be used) at screening and D1 of each cycle if abnormal at baseline.
[l] Serum β-hCG (for all FCPB) performed at screening; remaining pregnancy tests may be serum or urine at the Investigator's discretion. Pregnancy testing (for all FCPB) must be done within 72 hours prior to the first administration of IP and prior to dosing on Day 1 of every cycle. If the serum screening pregnancy test is performed > 72 hours before first dose, a serum or urine pregnancy test should be performed (Investigator's discretion). The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative.
[m] Day 1 of Cycle 3 and every third cycle thereafter (C6D1, C9D1, C12D1)
[n] On Cycle 1 Day 1, pembrolizumab will be administered after the 6 hour CC-486 PK sample collection. For all subsequent pembrolizumab administration, pembrolizumab will be co-administered with CC-486.

6. PROCEDURES

Any questions regarding the study should be directed to the Celgene medical monitor or designee.

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dosing unless noted below. Re-screening of patients is only allowed once per patient.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses will be performed centrally. Decisions with respect to investigational product (IP) dosing can be made based on a local lab draw if the central lab results have not been received. Central labs should be drawn at all times specified within the protocol. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window if necessary.

The following will be performed at screening as specified in the Table of Events (Table 2), after informed consent has been obtained:

- Demographics
- Prior cancer history (including specific information regarding diagnosis, staging, and histology)
- Prior cancer therapies: includes surgery, radiation, systemic or any other therapy for the subject's cancer
- Complete medical history (all relevant medical conditions occurring ≥ 28 days before Screening should be included)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before screening, except for those taken for cancer which are recorded as part of prior cancer therapy)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before screening)
- Interactive response technology (IRT) for subject number
- Adverse event evaluation (begins after the subject signs the informed consent form [ICF])
- Physical examination (source documented only), weight, height
- Vital signs (including blood pressure, temperature, respiratory rate, and heart rate)
- Eastern Cooperative Oncology Group (ECOG) performance status

- Hematology panel: Complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count.
- Coagulation tests including, prothrombin time (PT), partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT), international normalized ratio (INR).
- Chemistry panel including, but not limited to sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, fasting glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin (indirect and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
- Lipid panel including total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides
- Thyroid test
- Hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies (hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg], hepatitis B surface antibody [HBsAb], hepatitis B e antibody [HBeAb], hepatitis B core antibody [HBcAb], hepatitis C virus antibody [HCVAb]
- Urinalysis (a urine dipstick may be used) at screening (and Day 1 of each cycle if abnormal at baseline).
- 12-lead electrocardiogram (ECG)
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta subunit of human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the serum pregnancy test did not already occur within 72 hours of dosing (negative results required for IP administration).
- Submission of archival or newly obtained tumor biopsy specimen for biomarker analysis is mandatory.
- Response assessment/tumor evaluation (see Section 6.4)

6.2. Treatment Period

The subjects must start treatment within 28 days of signing the ICF. For all subsequent visits, an administrative window of ± 2 days is permitted.

Treatment cycles are 21 days in duration, and will occur as described in Section 8.2.

The following evaluations will be performed at the frequency specified in Table 2. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- IRT for subject randomization (prior to first dose)
- Concomitant medications evaluation (continuously)
- Concomitant procedures evaluation (continuously)
- Adverse event evaluation (continuously)
- Physical examination (source documented only) including weight
- Vital signs: on-treatment vital sign measurements will be source documented only. However, if an abnormal (out of range) value is reported at any given visit, that parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal, and as an AE if appropriate.
- ECOG Performance status
- Hematology panel
- Chemistry panel
- Lipid panel
- Thyroid test
- Urinalysis
- Urine (or serum) pregnancy test (prior to dosing on Day 1 of each cycle)
- PK sampling
- Tumor biopsy for biomarker analyses [Optional, but strongly recommended]
- Blood for biomarker analyses
- Serum for biomarker analyses
- Saliva for Germline DNA Analysis
- Response assessment/tumor evaluation (see Section 6.4)
- IP accountability

6.2.1. End of Treatment

An end of treatment (EOT) evaluation should be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. Subjects must also be discontinued in the IRT system.

The following evaluations will be performed as specified in the Table 2:

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event evaluation (monitored through 30 days after the last dose of either study drug)
- Physical examination including weight

- Vital signs
- ECOG performance status
- Hematology panel
- Hepatitis B virus (HBV) and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb
- Chemistry panel
- Lipid panel
- Urinalysis
- 12-lead ECG
- Urine (or serum) β-hCG level for females of childbearing potential
- Blood for biomarker analyses
- Serum for biomarker analyses
- Response assessment/tumor evaluation will be continued at the schedule defined in Table 2, and does not need to be performed specifically for the EOT visit except as specified in Section 6.4.
- IP accountability

6.3. Follow-up Period

6.3.1. Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, start of new anticancer therapy, or withdrawal of consent from the entire study will be followed for tumor response assessments and subsequent anticancer therapies as specified in Section 6.4.

6.3.2. Survival Follow-up

After the end of treatment (EOT) visit, all subjects will be followed every 8 weeks (± 5 days) for survival until withdrawal of consent, death, or lost to follow-up, whichever occurs first, or until the End of Trial. Subsequent anticancer therapies should be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or local medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

6.4. Response Assessments

Response assessments (tumor evaluations) should be performed at Screening within 28 days before the start of IPs, and every 6 weeks (± 5 days) from randomization for the first 24 weeks, then every 9 weeks thereafter until disease progression (for exceptions refer to Section 6.4.3), start of a new anticancer therapy, or withdrawal of consent from the entire study. Tumor assessments should also be performed at any time, if clinically indicated. Subjects with

historical tumor scans evaluable per RECIST 1.1 performed ≤ 28 days before the first dose need not repeat scans for the purposes of screening. Evaluation of response should be performed using RECIST 1.1 and irRECIST guidelines by Investigator assessment.

6.4.1. Assessment of Response According to RECIST Version 1.1

Response assessments include computed tomography (CT) scan or MRI. The regions to be imaged are the chest, upper abdomen including whole liver and kidney and, if clinically indicated, pelvis. The pelvis scan should be performed only with MRI unless CT is the local standard of care at the site. In case of metastases to other organs not covered with these scans, the regions need to be included in the scans as well. If brain metastases are documented at baseline, brain imaging should be continued throughout the study. Bone scans will only be performed at baseline if clinically indicated. If at baseline, the bone scan is suggestive of bone lesions, CT or MRI will be used both at baseline and subsequent scans. Bone scans during the trial will only be performed if clinically indicated and if suggestive of new lesions, a CT or MRI will be performed to confirm the new lesion. Any skeletal lesions identified at baseline should be followed at the same schedule. The same mode of imaging for lesion evaluation at Screening must be used consistently throughout the study. Adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments; scans must follow the calendar and not be adjusted for delays in treatment.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks.

6.4.2. Assessment of Response According to irRECIST

Evaluation of response will also be performed using irRECIST guidelines as an exploratory assessment. Additional details and definitions of irRECIST are found in Appendix B in Section 19.2.

6.4.3. Assessment of Disease and Treatment after Initial Radiologic Progression

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD by RECIST 1.1, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD (per irRECIST) with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. A separate informed consent will be provided. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted in Table 3). In determining whether or not the tumor burden has increased or decreased,

Investigators should consider all target lesions as well as non-target lesions. Refer to Appendix B for additional information.

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the 1st evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in Table 3. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Table 3: Imaging and Treatment after Site-Assessed 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Site based assessment indicates PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required Exceptions as per note*	Discontinue treatment Exceptions as per note*	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

* Note: If progression is confirmed per irRECIST, the subject remains clinically stable and per the Principal Investigator is achieving extraordinary clinical benefit, the Principal Investigator may discuss with the Sponsor to consider a potential exception.

6.5. Pharmacokinetics

At specific sites, for the first 10-12 subjects randomized to each Arm, mandatory pharmacokinetics will be collected. Blood samples for CC-486 PK assessment will be collected on Day 1 of Cycle 1 and Cycle 2 prior to the dose administration of CC-486/placebo, known as predose, and over the 8-hour period following each dose administration of CC-486/placebo at

0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose (see Table 4). These samples will be analyzed centrally.

Table 4: Schedule of Pharmacokinetic Blood Sample Collection in the Pharmacokinetics Phase

Nominal Times	Acceptable Deviation Window
Predose	≤ 60 min
0.25 hr	± 3 min
0.5 hr	± 3 min
1 hr	± 3 min
1.5 hr	± 3 min
2 hr	± 3 min
2.5 hr	± 3 min
3 hr	± 3 min
3.5 hr	± 3 min
4 hr	± 3 min
6 hr	± 20 min
8 hr	± 20 min

6.6. Biomarkers

Tumor, blood and serum will be collected to explore the hypothesized mechanism of CC-486 priming to pembrolizumab efficacy, and potentially identify biomarkers to predict patients that would benefit from this therapeutic regimen. Fresh tumor biopsy is the preferred tissue for these analyses; however archival formalin fixed, paraffin embedded (FFPE) blocks may be provided instead. Archival or fresh tumor tissue is mandatory at screening, but it is optional at Cycle 2 Day 14 -/+ 7 days. Blood, serum and saliva will also be collected at time point detailed in the schedule of events.

Details regarding the collection, storage, and shipment of the samples are provided in the Laboratory Manual. A separate consent will be provided.

6.7. 12-lead Electrocardiogram

Triplicate 12-lead ECGs will be recorded at screening and EOT and will be assessed locally. ECGs may be done more frequently and/or additional cardiac work-up may be performed, if clinically indicated by the investigator. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and QTc interval) will be performed after the subject has been in the supine position for at least 5 minutes.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

A total of approximately 90 adult subjects with locally advanced or metastatic NSCLC who have been treated with one prior platinum-based chemotherapy regimen will be randomized. The study will be conducted at sites globally.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent form.
2. Subject has histologically or cytologically confirmed squamous or non-squamous NSCLC.
3. Subject has stage IIIB or IV NSCLC (American Joint Committee on Cancer [AJCC] Staging Manual, 7th edition [Edge, 2009]) and was pretreated with only 1 prior systemic platinum based chemotherapy.
4. Subject has provided a formalin fixed tumor tissue sample from a biopsy of a tumor lesion either at the time of or after the diagnosis of metastatic disease has been made AND from a site not previously irradiated to assess for PD-L1 status. Fine needle aspirates, endobronchial ultrasound (EBUS) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required. Archival tissue may be acceptable. Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.
5. Subject has radiographically-documented measurable disease, as per RECIST 1.1.
6. Subject has an ECOG performance status of 0 to 1.
7. Subject has adequate organ functions, evidenced by the following:
   a. AST (SGOT), ALT (SGPT) ≤ 2.5 x upper limit of normal range (ULN), or ≤ 5 x ULN range if liver metastasis present
   b. Total bilirubin ≤ 1.5 x ULN
   c. Serum creatinine ≤ 1.5 x ULN
   d. Potassium within normal range, or correctable with supplements
8. Subject has adequate bone marrow function, evidenced by the following:
   a. Absolute neutrophil count ≥ 1.5 x 10^9 cells/L
   b. Platelets ≥ 100 x 10^9 cells/L
   c. Hemoglobin ≥ 9 g/dL
   d. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

e. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

9. Female of childbearing potential (FCBP) (defined as a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or, 2) if ≥ 45 years old has 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 two negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.

   b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with two effective methods of contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 120 days after discontinuation (or longer if required by local requirements) of study therapy. The two methods of contraception can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy.

10. Male subjects must practice true abstinence* (which must be reviewed on a monthly basis) or agree to the 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 3 months following investigational product discontinuation (or longer if required by local requirements), even if he has undergone a successful vasectomy.

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

11. Subject is willing to adhere to the study visit schedule and other protocol requirements.
12. Subject understands and voluntarily signs an informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subject with non-squamous histology has known or unknown sensitizing EGFR and/or positive ALK mutation.

   Note: Subjects with squamous histology and unknown EGFR and ALK mutational status are eligible.

2. Subject has received more than one line of therapy for stage IIIB or IV disease
3. Subject has been previously treated with azacitidine (any formulation), decitabine, or any other hypomethylating agent.

4. Subject has received prior therapy with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanism, including participation in any other pembrolizumab trial and treatment with pembrolizumab.
    a. Examples of such antibodies include (but are not limited to) antibodies against indoleamine 2,3-dioxygenase (IDO), PD-L1, IL-2R, glucocorticoid-induced tumor necrosis factor receptor (GITR).
5. Subject has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Subject is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of pembrolizumab and CC-486
7. Subject has previous severe hypersensitivity reaction to another monoclonal antibody (mAb).
8. Subject has a known or suspected hypersensitivity to azacitidine, mannitol, or any other ingredient used in the manufacture of CC-486 (see the Azacitidine IB).
9. Subject has had 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.
10. Subject has received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment
11. Subject has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
12. Subject has not recovered from the acute toxic effects of prior anticancer therapy, radiation, or major surgery/significant trauma.
13. Subject has an active infection requiring therapy.
14. Subject has had an allogenetic tissue/solid organ transplant.
15. Subject has active autoimmune disease that has required systemic treatment within the past 2 years (eg, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
16. Subject has known active Hepatitis B, Hepatitis C or tuberculosis. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV ribonucleic acid (RNA) results greater than the lower limits of detection of the assay.
17. Subject has had any other malignancy within 5 years prior to randomization, with the exception of adequately treated in situ carcinoma of the cervix, uterus, or non-melanomatous skin cancer (all treatment of which should have been completed 6 months prior to enrollment).

18. Subject has a history of inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), celiac disease (ie, sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism, or excretion of the IP and/or predispose the subject to an increased risk of gastrointestinal toxicity.
19. Subject has persistent diarrhea or clinically significant malabsorption syndrome or known sub-acute bowel obstruction ≥ Grade 2, despite medical management
20. Subject has significant active cardiac disease within the previous 6 months including unstable angina or angina requiring surgical or medical intervention, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure.
21. Subject has history of interstitial lung disease (ILD) OR a history of pneumonitis that has required oral or IV steroids. Subjects whose pneumonitis was solely as a result of radiation therapy for their NSCLC would not be excluded from the study unless they received oral/IV steroids to manage the pneumonitis.
22. Subject has a known history or current diagnosis of human immunodeficiency virus (HIV) infection, regardless of treatment status.
23. Subject has any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment, contraindicate patient participation in the clinical study (eg, chronic pancreatitis, etc.).
24. Subject with uncontrolled or symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis
    - Subjects with controlled and asymptomatic CNS metastases may participate in this trial. The patient must have completed any prior treatment for CNS metastases (must include radiotherapy and/or surgery) ≥ 28 days (≥ 14 days for stereotactic radiosurgery). Patients must not be receiving corticosteroids for brain metastases.
25. Subject has not recovered from the acute toxic effects (Common Terminology Criteria for Adverse Events [CTCAE] grade ≤ 1) of prior anticancer therapy, radiation, or major surgery/significant trauma (except alopecia or other toxicities not considered a safety risk for the subject at the Investigator's discretion).
26. Subject has an impaired ability to swallow oral medication.
27. Subject is pregnant or breast feeding.
28. Subject has any condition that confounds the ability to interpret data from the study.
29. Subject is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

Subjects will receive CC-486 plus pembrolizumab or pembrolizumab plus placebo during the study. CC-486 and matching placebo will be double blind whereas pembrolizumab will be open label. CC-486 and pembrolizumab are designated as IPs. All IPs must be stored in an area free of environmental extremes and a secured area to prevent unauthorized access, as directed on the package label. A temperature log must be maintained.

8.1.1. CC-486 (Oral Azacitidine)/Placebo

The study sponsor, Celgene Corporation will supply CC-486 and placebo 150 and 200-mg tablets for oral administration. Sufficient quantities of IP will be supplied by Celgene and should be stored as directed on the label. All tablets will be packaged in blister packs. Each tablet is formulated using excipients that are generally regarded as safe and used in marketed drug products. A list of excipients included in the formulations is provided in the azacitidine IB.

8.1.2. Pembrolizumab

Pembrolizumab (50 mg lyophilized powder in single-use vial for reconstitution) for IV administration will be sourced by the study sponsor (Celgene Corporation) from and labeled for clinical trial use. Sufficient quantities of IP will be supplied by Celgene and should be stored as directed on the label. Pembrolizumab will be administered in the clinic.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.2. Treatment Administration and Schedule

Subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or pembrolizumab plus placebo. CC-486/placebo will be administered at a dose of 300 mg orally daily on days 1-14 of a 21-day cycle.

During scheduled site visits the subjects must arrive to the clinic in the fasting state (ie, no food or drink [except water] for approximately 8 - 10 hours) for all predose safety laboratory evaluations. Dose administration should take place after all scheduled predose safety assessments are completed.

Subjects will ingest CC-486/placebo with approximately 240 mL (8 ounces) of room temperature water. CC-486/placebo may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories).

If following CC-486/placebo administration an emesis event occurs, subjects should not take additional drug on that same day. It is recommended that the subject receives an antiemetic 30 minutes prior to all subsequent CC-486 doses.

Pembrolizumab will be administered as a 30-minute IV infusion at a dose of 200 mg (4 x 50 mg vials) on Day 1 of a 21-day cycle. Sites should make every effort to target infusion timing to be

as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time of 24-40 minutes). Pembrolizumab should be co-administered with CC-486.

For subjects enrolled in the PK population, the treatment administration on PK days (i.e., Day 1 of Cycle 1 and Cycle 2) is described below:

- After performing the required overnight fast, taking antiemetic premedication with 240 mL of water for nausea and vomiting (eg, ondansetron), and completing the required predose assessments (including the predose PK sample), subjects will ingest CC-486/placebo with 240 mL of room temperature water in the clinic approximately 30 minutes after antiemetic administration on each PK dosing day. Each dose of CC-486/placebo should be given at approximately the same time each day. The exact date and time of dosing will be recorded in the source documents and appropriate CRF.
- On Day 1 of Cycle 1 only, pembrolizumab will be administered as described above, but administration will start after the 6 hour CC-486 PK sample collection time-point.

Dietary restrictions on PK days (i.e., Day 1 of Cycle 1 and Cycle 2):

- Subjects should be instructed to limit their coffee intake to one 8-ounce cup of black coffee (no cream or sugar) and to not consume alcohol, tea, chocolate, or cola beverages within 2 hours prior to collecting PK samples.
- Subjects should not ingest food for a minimum of 8 hours prior and 2 hours after CC-486/placebo is administered. Water can be allowed as desired except for 1 hour before and after CC-486/placebo administration. The only water permitted in the 1-hour period before CC-486/placebo administration is the 240 mL of water for antiemetic ingestion.

8.2.1. Dose Adjustment Guidelines

8.2.1.1. CC-486 (oral azacitidine)/Placebo

For CC-486/placebo, a maximum of 1 dose reduction will be allowed from the original dose (eg, patients can dose reduce from 300 mg/placebo oral daily dose to 200 mg/placebo oral daily dose). Re-escalation to the higher dose is not permitted. If a subject requires more than 1 dose reduction for CC-486/placebo, they will be discontinued from CC-486/placebo, however, they may continue to receive pembrolizumab (and conversely, subjects who discontinue pembrolizumab may continue to receive CC-486/placebo) but must continue to undergo all safety and efficacy assessments as per Table 2.

CC-486/placebo may be withheld for up to 7 days between the end of 1 cycle and the start of the next cycle to allow hematologic criteria to recover sufficiently for the next cycle to begin.

The maximum number of days that a dose may be withheld without requiring a dose reduction is 7 days.

The maximum number of days that a dose may be withheld due to unacceptable toxicity before a subject is permanently discontinued from CC-486 is 14 days. For the purposes of dose adjustments, unacceptable toxicity will be defined as any AE that is deemed by the Investigator

to be related to CC-486/placebo that poses a medical risk or substantial discomfort to the subject including, but not limited to, Grade 3 or 4 hematologic or non-hematologic toxicity. Subjects should be discontinued after the 3rd episode.

See Section 8.2.1.2 and Table 6 for dose modification guidelines for pembrolizumab drug-related adverse events for overlapping toxicity events for all IPs.

Please refer to Table 5 for the Dose Adjustment Guidelines.

Table 5: CC-486/Placebo Dose Adjustment and Dose Delays for Toxicity

Toxicity	Recommendation
Grade 2 hematologic toxicity causing delay to the planned start of a Cycle Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L Platelets < 75 x 10^9/L	Hold CC-486/placebo until ANC & Platelets ≤ Grade 1 Delay ≤ 7 days, resume CC-486/placebo at same dose Delay 8 – 14 days, reduce CC-486/placebo by 100 mg Delay > 14 days, permanently discontinue from study
Grade 3 neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC 0.5-0.99 x 10^9/L Platelets 25-49 x 10^9/L	Hold CC-486/placebo until ANC & Platelets recover to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, resume CC-486/placebo at same dose Recovery in 8–14 days, reduce CC-486/placebo by 100 mg No recovery by 14 days, permanently discontinue from study
Grade 4 neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC < 0.5 x 10^9/L Platelets < 25 x 10^9/L For ANC < 0.5 x 10^9/L The initiation of G-CSF is left at the Investigator's discretion. If initiated administer G-CSF per institutional practice or package insert and continue until ANC recovers to ≥ 2.0 x 10^9/L	Hold CC-486/placebo until ANC & Platelets recover to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, reduce CC-486/placebo by 100 mg No recovery by 7 days, permanently discontinue from study

Table 5: CC-486/Placebo Dose Adjustment and Dose Delays for Toxicity (Continued)

Toxicity	Recommendation
Grade 3 or 4 Nausea or Vomiting Grade 3 or 4 Diarrhea Grade 3 or 4 Fatigue/Asthenia	Hold until resolution to ≤ Grade 1 and provide optimal medical management If response ≤ 72 hours (3 days), and recovery ≤ 7 days, reintroduce CC-486/placebo at 200 mg If event recurs after re-challenge at 200 mg, discontinue CC-486/placebo If no recovery by 7 days, discontinue CC-486/placebo
Grade 3 or 4 any other non-hematologic toxicity	Hold until resolution to ≤ Grade 1 and provide optimal medical management If recovery ≤ 7 days, reintroduce CC-486/placebo at 200 mg If event recurs after re-challenge at 200 mg, discontinue CC-486/placebo If no recovery by 7 days, discontinue CC-486/placebo
Renal dysfunction - For any unexplained reductions in serum bicarbonate levels to < 20 mEq/L or unexplained elevations of BUN and/or serum creatinine (> 20%) from baseline	Hold until resolution to ≤ baseline level (+/- 20%) Reduce CC-486 dose in the next cycle of treatment to the next lower dose level If similar unexplained renal and/or electrolyte disturbances subsequently persist or recur, discontinue CC-486

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; BUN = blood urea nitrogen; ESMO = European Society for Medical Oncology; G-CSF = granulocyte colony stimulating factor.
Note: The initiation of G-CSF is left at the Investigator's discretion.
Note: Granulocyte colony stimulating factor (G-CSF) should only be utilized in accordance to ASCO or ESMO recommendations.
Note: If Grade 3 or 4 neutropenia associated with fever or Grade ≥ 3 thrombocytopenia with clinically significant bleeding occurs at any time, the dose adjustment guidelines for Grade 4 hematological toxicity should be enacted.
Note: If neutropenia is associated with fever and severe diarrhea, subject should be managed appropriately according to the local practice. In case of recurrence of the diarrhea with neutropenia and fever, the continuation of the subject in the study should be discussed on a case-by-case basis with the sponsor's study monitor.

8.2.1.2. Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 6 below. Dose reductions are not permitted for pembrolizumab.

Table 6: Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (T1DM), if new onset, or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue

Table 6: Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events (Continued)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold IP at physician discretion. Permanently discontinue IP for persistent Grade 2 adverse reactions for which treatment with IP has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

After the first cycle, each drug may be given independently on a cyclical regimen according to the protocol-defined dose interruptions/delays for CC-486/placebo or pembrolizumab as defined in Section 8.2.1 above. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.2.2. Overdose

Overdose, as defined for this protocol, refers to blinded CC-486 and/or pembrolizumab.

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (5 times the dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For CC-486, on a per dose basis, an overdose is defined as any amount over the protocol-specified dose of blinded CC-486 assigned 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.

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

8.3. Method of Treatment Assignment

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will be randomized by IRT to receive CC-486 plus pembrolizumab or placebo plus pembrolizumab. Treatment assignment will be performed centrally.

All IP will be managed by the IRT system as a central subject number assignment and accountability tool only.

8.4. Packaging and Labeling

The labels for IPs may include, but are not limited to, 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.

8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site versus the responsibilities of Celgene (or designee).

8.6. Investigational Product Compliance

Accurate recording of all IPs administered will be made in the appropriate section of the subject's case report form (CRF) and source documents. The Investigator or designee is accountable for the compliance of all study-specific IPs either administered or in their custody during the course of the study.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

9.1.1. CC-486 (oral azacitidine)

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted.

All concomitant treatments, including blood and blood products, must be reported on the CRF.

Subjects may be administered supportive and palliative care (eg, pain control, anti-nausea, anti-diarrheal) as clinically indicated throughout the study.

Myeloid growth factors (granulocyte colony stimulating factor [G-CSF] and granulocyte macrophage colony-stimulating factor [GM-CSF]) should be administered according to American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines only for the treatment of neutropenic infections.

Antiemetic administration is encouraged during the study, and is required for subjects enrolled in the PK population; at the Investigator's discretion, subjects not enrolled in the PK population may receive prophylactic antiemetic therapy (eg, a serotonin [5-HT3] receptor antagonist such as ondansetron) approximately 30 minutes prior to each dose of CC-486.

Treatment with antidiarrheal medications should be prescribed at the first sign of diarrhea. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate at the Investigator's discretion.

9.1.2. Pembrolizumab Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

> Note: if after the evaluation the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 6 for dose modification guidelines for pembrolizumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.1.2.1. Management of pneumonitis

These guidelines may also be used for cases of pneumonitis that may not be related to pembrolizumab.

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration

9.1.2.2. Management of Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.1.2.3. Management of type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For type 1 diabetes mellitus (T1DM) or Grade 3-4 Hyperglycemia
  - Insulin replacement therapy is recommended for type 1 diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

9.1.2.4. Management of hypophysitis

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be

started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.1.2.5. Management of hyperthyroidism or hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Grade 3-4 hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.1.2.6. Management of hepatic abnormalities

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

9.1.2.7. Management of renal failure or nephritis

- For Grade 2 events, treat with corticosteroids.
- For Grade 3-4 events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.1.2.8. Management of infusion reactions

Table 7 shows treatment guidelines for subjects who experience an infusion reaction associated with the administration of pembrolizumab.

Table 7: Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5 hrs. (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).

Table 7: Infusion Reactions (Continued)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

CTCAE = Common Terminology Criteria for Adverse Events; hr = hour; IV = intravenous(ly); NCI = National Cancer Institute; NSAID = non-steroidal anti-inflammatory drug; p.o. = oral(ly)
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.
For Further information, please refer to CTCAE v4.0 at http://ctep.cancer.gov

9.2. Prohibited Concomitant Medications and Procedures

The following concomitant medications are prohibited during the course of the study:

- Cytotoxic, chemotherapeutic, targeted, hormonal, or investigational agents/therapies or any other anticancer treatment.
- Vidaza (azacitidine injection), decitabine, or other demethylating agents.
- Other PD-1 or PD-L1 inhibitors
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with

Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, bacillus Calmette-Guerin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest (ECI), use as a pre-medication for chemotherapeutic agents specified in the protocol, or for use as a pre-medication in subjects with a known history of an IV contrast allergy administered as part of CT radiography. Replacement doses of steroids (for example, prednisone 5-7.5 mg daily) are permitted while on study. Subjects who, in the assessment by the Investigator, require the use of corticosteroids for any other clinical management should be discussed with medical monitor.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a placebo-controlled, double-blind, randomized, phase 2 trial designed to estimate the efficacy and safety/tolerability of CC-486 plus pembrolizumab and placebo plus pembrolizumab, in subjects with previously treated metastatic non-small cell lung cancer. The primary endpoint is PFS based on Investigator review.

The sections below lay out the proposed statistical considerations and analyses. The detail statistical analysis methods will be documented in the statistical analysis plan (SAP).

10.2. Study Population Definitions

10.2.1. Intent-To-Treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects. All efficacy analyses will be based on the ITT population, unless otherwise specified. The efficacy analyses will be performed according to treatment assigned at randomization.

10.2.2. Safety Population

The safety population will consist of any enrolled subjects who received at least 1 dose of IP. All safety analyses will be based on the Safety population, unless otherwise specified. The treatment groups for the safety analyses are based on the treatment as received if different from the pre-planned randomization.

10.2.3. PK Population

The PK analysis population will include all randomized subjects who have evaluable concentration data to determine the pharmacokinetic parameters from at least 1 dose of CC-486.

10.2.4. Biomarker Population

The biomarker analysis population will include all randomized subjects who received at least 1 dose of IP, provided consent for exploratory biomarker studies, and had at least 1 predose biomarker tissue collected and deemed of adequate quality for biomarker analysis.

10.3. Sample Size and Power Considerations

The primary goal of this study is to provide estimates of the difference in efficacy and safety between CC-486 plus pembrolizumab and placebo plus pembrolizumab.

Approximately 90 subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or placebo plus pembrolizumab. Primary analysis will be conducted when 70 PFS events occur.

Selected hypothetical scenarios are presented in Table 8 with confidence interval and power estimates, when approximately 70 PFS events have occurred.

The table below demonstrates the hypothetical power of testing the null hypothesis H_0: $\lambda_T/\lambda_C=1$, against the two sided alternative H_0: $\lambda_T/\lambda_C\neq1$,assuming that time to PFS events in both treatment

arms follow exponential distributions, and λ_C is the monthly hazard rate of the survival distribution in the control arm, and λ_T is the monthly hazard rate of the survival distribution in the experimental arm (CC-486+pembrolizumab).

Table 8: Hypothetical Power and Resulting Two-sided 90% CI of Hazard Ratio

Combo Treatment Median PFS (month)	5.5	5.0	4.6
Total PFS events	74	75	76
Power (%) w/two-sided α=0.10[1]	82.4	71.7	59.4
HR with [two-sided 90% CI]	0.55 [0.38,0.81]	0.60 [0.41,0.88]	0.65 [0.45,0.95]

[1] These calculations assume the median PFS in pembrolizumab alone is 3.0 months (Garon, 2014). And lost to follow-up (to assess PFS events) rate is 10% at the end of study.

The power calculations are conducted with East 5.4.

10.4. Background and Demographic Characteristics

Subjects' 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. 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 phases. 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 Endpoint

The primary endpoint PFS will be defined as the time from the randomization date to disease progression assessed by Investigator according to RECIST version 1.1 guideline or death due to any cause, whichever occurs first.

Subjects who are alive and progression-free at the cut-off date of the PFS analyses will be censored at the date of the last tumor evaluation. If subjects begin new anti-cancer therapy prior to documented progression, PFS will be censored at the last assessment prior to receiving the anti-cancer therapy. Subjects with 2 or more missing response assessments prior to a visit with documented disease progression (or death) will be censored at the last visit where the subject was documented to be PFS event-free. A sensitivity analysis will be performed with censoring rules that follow the principles of assigning the date of event based on the time of the first evidence of objective progression or death regardless of violations, discontinuation of IP or change of therapy.

PFS will be summarized by median progression-free survival time (including two-sided 90% confidence interval [CI]) for each treatment group and within each strata. The hazard ratio and a

two-sided 90% CI will be estimated by using Cox proportional hazard model with treatment, and any stratification factors as model covariates. The Kaplan-Meier curve for PFS will be presented for each treatment group and strata.

10.6.2. Secondary Endpoints

10.6.2.1. Overall Survival

Overall survival (OS) will be defined as the time from the date of randomization to the date of death (any cause). Subjects who are alive will be censored at the last time that the subject was known to be alive. The OS analysis may also be conducted at the time when 70 deaths occur, in addition to when the primary analysis is performed.

Medians of overall survival including two-sided 90% CI for each treatment group will be calculated. The hazard ratio and a two-sided 90% CI will be estimated using Cox proportional hazard model with treatment, and all stratification factors in the model. The Kaplan-Meier curve for survival will be presented for each strata and treatment group.

10.6.2.2. Overall Response Rate (ORR)

Overall response rate is the percentage of subjects that achieve a confirmed complete or partial response as assessed by the Investigator using RECIST version 1.1 guideline. This rate will be presented for each treatment group and strata. The 90% CI of the response rates will be provided. A two-sided 90% CI of the Response rate differences between pembrolizumab plus placebo and pembrolizumab plus CC-486 arm, with each strata and overall will be provided.

10.6.2.3. Disease Control Rate (DCR)

The percentage of disease control (i.e., confirmed SD, CR or PR) according to RECIST 1.1 will be analyzed in the same manner as ORR. When SD is believed to be best response, it must meet the minimum duration of 18 weeks from randomization.

10.6.2.4. irPFS, irORR and irDCR per irRECIST

Exploratory endpoints such as irPFS, irORR, and irDCR assessed by Investigator according to irRECIST will be analyzed using statistical methods described previously for similar primary or secondary endpoints.

10.6.3. Subgroup Analysis

The effect of treatment on the efficacy variable OS, PFS, and DCR may be investigated within subgroups defined by selected baseline prognostic variables and any stratification factors.

The methods described in previous statistical analysis sections will be used for each subgroup separately. A forest plot may also be provided.

10.7. Safety Analysis

Safety analysis will be performed using the safety population. Safety and tolerability will be monitored through continuous reporting of all AEs and SAEs, laboratory abnormalities, and incidence of subjects experiencing adverse events resulting in dose reductions, dose

interruptions, and/or premature discontinuation of study drugs. TEAEs, TEAEs leading to death or discontinuation from treatment, events assessed as Grade 3 or Grade 4, events of clinical interest, vital signs, weight, clinical laboratory information, and concomitant medications/procedures will be tabulated and summarized.

Treatment-emergent adverse events will be coded according to MedDRA. All TEAEs will be summarized by MedDRA system organ class and preferred term, frequency, severity grade based on the CTCAE (Version 4.0) and relationship to treatment. Serious adverse events, events of clinical interest, and events leading to discontinuation or death will be listed separately.

10.8. Pharmacokinetic Analysis

When appropriate, plasma PK samples collected will be analyzed for CC-486 concentration determination using a validated high-performance liquid chromatography/tandem mass spectrometric method.

10.8.1. Plasma Concentrations

By-subject listing of pharmacokinetic blood sample collection times as well as derived sampling time deviations will be provided. CC-486 plasma concentrations will be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each cycle, if/when appropriate. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Missing concentrations and concentrations from blood samples collected more than ± 10% of nominal time will be omitted from the calculation of descriptive statistics.

Individual subject concentration-time data and mean concentration-time data for each cycle will be graphically presented on linear and semi-logarithmic scales.

Following single dose administration, predose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at predose will be identified in the clinical study report (CSR) and used for the computation of AUC. Pharmacokinetic parameters will be computed if the anomalous value is not greater than 5% of the C_{max}. If the anomalous value is greater than 5% of C_{max}, the computed pharmacokinetic parameters for the given subject will be dropped from the pharmacokinetic analysis.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating AUC. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the pharmacokinetic analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile. For the purpose of analysis, these trailing BLQ values may be designated as zero in the dataset if the pharmacokinetic program

used to do the analysis (such as WinNonlin®) will treat trailing zero values as missing when calculating AUC.

Actual sampling times will be used in the calculations of pharmacokinetic parameters that will be derived using noncompartmental methods with Phoenix™ WinNonlin® Professional Version 6.3, or higher, Graphics may be prepared with SAS Version 9.1, or higher; or Excel 2007, or higher; Phoenix™ WinNonlin® Professional 6.3, or higher; or S-Plus 8.2., or higher .

10.8.2. Pharmacokinetic Parameters

The following PK parameters will be calculated for CC-486:

AUC_{inf}	Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as $[AUC_t + Ct/\lambda_z]$. Ct is the last quantifiable concentration. No AUC extrapolation will be performed with unreliable λ_z. If AUC %Extrap is ≥25%, AUC_{inf} will not be reported
AUC_t	Area under the plasma concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.
C_{max}	Maximum observed plasma concentration, obtained directly from the observed concentration versus time data.
T_{max}	Time to C_{max}, obtained directly from the observed concentration versus time data.
$t_{1/2}$	Terminal phase half-life in plasma, calculated as $[(\ln 2)/ \lambda_z]$. $t_{1/2}$ will only be calculated when a reliable estimate for λ_z can be obtained.
CL/F	Apparent total clearance, calculated as $[Dose/AUC_{inf}]$.
Vz/F	Apparent volume of distribution, calculated as $[(CL/F)/\lambda_z]$.

The following PK parameters for CC-486 will be calculated for diagnostic purposes and listed, but they will not be summarized:

λz	Apparent terminal rate constant, calculated by linear regression of the terminal portion of the log-concentration versus time curve in plasma. Visual assessment will be used to identify the terminal linear phase of the concentration versus time profile. A minimum of three data points will be used for calculation. λz will not be estimated if the terminal phase of the log-concentration versus time profile does not exhibit a linear decline phase, or if the regression coefficient < 0.8.

λz lower	Lower limit of time (h) included in the calculation of λz.
λz N	Number of data points used in the calculation of λz.
λz upper	Upper limit of time (h) included in the calculation of λz.
Rsq	Regression coefficient for calculation of λz.
AUC % Extrap	Percentage of AUC_{inf} due to extrapolation from the last quantifiable time point to infinity.

10.8.3. PK Analyses

By-subject listing of pharmacokinetic parameters will be provided. The pharmacokinetic parameters will also be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each cycle. Also, when appropriate, graphical representations (i.e., scatter plots, box plots, etc) may be used to visualize the results.

The effect of pembrolizumab on the PK of CC-486 will be assessed using graphic comparison and descriptive stats.

Exploratory analysis may be conducted to investigate the relationship between PK parameters and efficacy endpoints.

10.9. Interim Analysis

No interim analysis of efficacy is planned for this study.

10.10. Other Topics

10.10.1. Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be established and will include medical oncologists and a statistician, all of whom are not otherwise involved in the study conduct. During the course of the study, the DMC will review the safety data regularly. The first DMC meeting will occur when 10 subjects in each arm have safety data from at least one cycle of treatment, with subsequent meetings approximately every 6 months or more often if requested by the DMC Chairman. The DMC will offer recommendations to continue, modify or stop the study based only on periodic evaluations of comparative safety data, in accordance with criteria outlined in the DMC Charter. An independent statistician will prepare the reports to the DMC members for each scheduled meeting. Operational details for the DMC will be detailed in the DMC charter.

10.10.2. Steering Committee

The conduct of this trial will be overseen by a Steering Committee (SC), presided over by the coordinating principal Investigator and if possible the representative regional Investigators from

countries participating in this study. The SC will serve in an advisory capacity to the Sponsor. Operational details for the SC will be detailed in a separate SC charter.

Note: The SC is separate from the DMC.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.2 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 CC-486 and pembrolizumab overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after the last dose of either study drug and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

In addition, events known as pembrolizumab Events of Clinical Interest (ECI) must also be recorded on the Adverse Event CRFs or Overdose CRF, depending on the event, and reported within 24 hours of the Investigator's knowledge of the event, regardless of whether or not the Investigator considers the event related to the IP. If the event meets serious criteria (SAE), the event must also be reported to Celgene Drug Safety also within 24 hours by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form as outlined in Section 11.5.

See Section 11.7 for detailed guidance on the reporting of pembrolizumab ECIs.

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 (i.e., 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 (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication, that has not worsened from baseline.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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 the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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

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

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:	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:	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 Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

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

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, 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 (returned to baseline), recovered with sequelae, 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, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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

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

11.4. Pregnancy

All pregnancies, suspected pregnancies and lactation occurring in either a female subject of childbearing potential or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential

Pregnancies, suspected pregnancies (including elevated β-hCG or a positive pregnancy test in a female of childbearing potential regardless of age or disease state) and lactation of a female subject that occur during the trial or within 120 days of completing the trial (or longer if required by local requirements), or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are considered immediately reportable events.

Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test, or lactation must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

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

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

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 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 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 taking investigational product becomes pregnant while the subject is receiving investigational product or within 3 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 their healthcare provider immediately. The female partner should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. Male subjects should avoid fathering a child until 3 months after the last dose of IP (or longer if required by local requirements). The ICF will address any country-specific requirements, as needed.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's

product must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drugs) that occur during the study (from the time the subject signs informed consent until 90 days after the last dose of either IP) or any SAE made known to the Investigator at anytime 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 should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

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

11.5.1. Safety Queries

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

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-486 based on the Investigator Brochure.

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

For countries within the European Economic Area (EEA), Celgene 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.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, pembrolizumab based on the Pembrolizumab Investigators Brochure for the product.

Events of disease progression for the disease under study (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.

Celgene 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 (i.e., 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 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. Pembrolizumab Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECIs and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's products, must be reported within 24 hours to the Sponsor, either by entering all ECIs of overdose on the Overdose CRF or by entering all other ECIs on the AE CRF within 24 hours of the Investigator's knowledge of the event, regardless of whether or not the Investigator considers the event related to the IP. If the event meets serious criteria (SAE), the event must also reported to Celgene Drug Safety within 24 hours by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form as outlined in Section 11.5.

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 8.2.2 - Overdose, that is not associated with clinical symptoms or abnormal laboratory results. See Section 11.1 for a description of how overdoses of pembrolizumab are to be documented (with or without associated adverse events).
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

* Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

12. DISCONTINUATIONS

12.1. Treatment Discontinuations

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

- Adverse Event
- Progressive Disease
- Symptomatic deterioration (global deterioration of health status)
- Physician decision
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other (to be specified on CRF)

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

The decision to discontinue a subject from treatment 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.

12.2. Study Discontinuation

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

- Adverse Event
- Progressive disease
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Other

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

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

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

13.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. IF it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IRT by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblended dose information.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

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

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

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

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene 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 Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene 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, Celgene 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 a subject and/or a subject's legal representative prior to any study related procedures.

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

14.4. Confidentiality

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

Should direct access to medical records require a waiver or authorization separate from the subject's signed 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 Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

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

Before the start of the study, the study protocol, 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 Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

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

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

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

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

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

14.8. Termination of the Study

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

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

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

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

15.2. Data Management

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

15.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- 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 Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Data Verification

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

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

16.2. Audits and Inspections

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

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

17. PUBLICATIONS

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

Celgene will ensure Celgene-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

19.1. Appendix A: RECIST 1.1

The following information is extracted/summarized from Eisenhauer, 2009, New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Please refer to the primary reference for further information.

19.1.1. Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

19.1.1.1. Measurable Disease

Tumor Lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

19.1.2. Tumor Response Evaluation

19.1.2.1. Target Lesions

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

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

19.1.2.2. Non-target Lesions

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

19.1.2.3. Response Criteria

Target and non-target lesions are evaluated for response separately, and then the tumor burden as a whole is evaluated as the overall response.

19.1.2.3.1. Target Lesion Response

Target lesions will be assessed as follows:

- Complete Response (CR). Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR). At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD). At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD). Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

19.1.2.3.2. Non-target Lesion Response

Non-target lesions will be assessed as follows:

- Complete Response (CR). Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD. Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD). Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the Subject Also Has Measurable Disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to quality for

unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Non-measurable Disease: This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so: therefore, the increase must be substantial.

19.1.2.3.3. Overall Response

Overall response should be assessed according to Table 9 for subjects with target lesions, and Table 10 for subjects with only non-target lesions.

Table 9: Time Point Response: Subjects With Target (± Non-target) Disease

Target Lesions Response	Non-target Lesion Response	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD[1]	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = inevaluable, PD = progressive disease, PR = partial response, SD = stable disease

Table 10: Time Point Response: Subjects With Non-target Disease Only

Non-target Lesion Response	New Lesions	Overall Response
CR	No	CR
Non-CR/ non-PD	No	Non-CR/non-PD1)[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, NE = inevaluable

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

19.1.2.4. Symptomatic Deterioration

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

19.2. Appendix B: irRECIST

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST

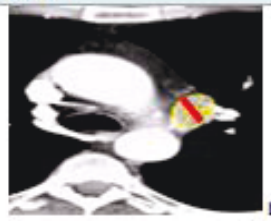
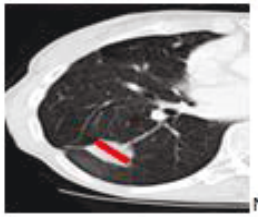
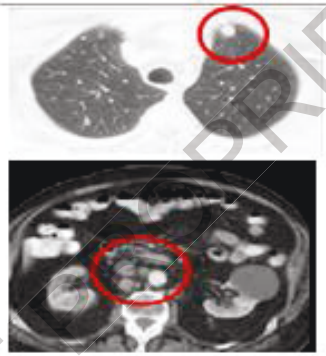
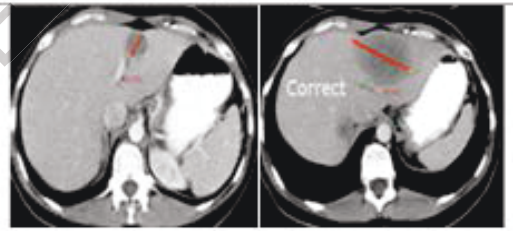
Standard RECIST 1.1	Images	Guidance
Target Lesion Selection at Baseline Must meet RECIST 1.1 measurability criteria Lymph nodes ≥ 15 mm in short axis Non-nodal lesions ≥ 10 mm in longest diameter Identify maximum of 5 target lesions, 2 per organ ▪ Nodes are considered an organ system Target lesion (TL) selection considerations: ▪ likely to be reproducible across all timepoints ▪ representative of tumor burden ▪ may include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation	 Lymph node-use short axis ≥ 15mm  Non nodal – use long axis≥ 10mm	For TLs, a measurement is required At Baseline report measurement of all TLs
Non-Target Lesion Selection at Baseline All other lesions including those that could meet measurability requirements. Non-target lesion (NT) selections: ▪ lesions which may not be reproducibly measured across all timepoints ▪ cystic lesions ▪ pleural/pericardial effusions and ascites ▪ bone lesions without measurable soft tissue ▪ it's possible to capture multiple NTs involving the same organ as a single item on the eCRF (e.g. multiple liver metastases)		Lesions at the lung apex or bases are often better to capture as non target because of the variability with inspiration. Clusters of lymph nodes that are measurable are often better to capture as non target because of the potential to coalesce. At Baseline report all NTs
Target Lesion Measurement at DLE2 Locate image that optimizes the longest diameter of the non-nodal target lesion or short axis of target node(s). There is no need to go to an identical slice from baseline.	 BL DLE2	SOD = sum of longest diameters (non-nodal) and short axis (nodal) of all TL **Note:** SOD is not reported to [redacted] from the sites

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

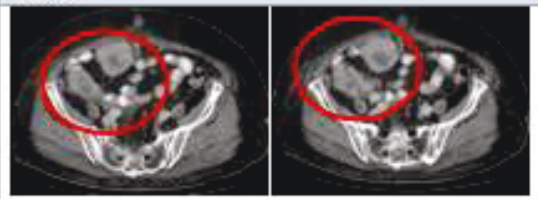
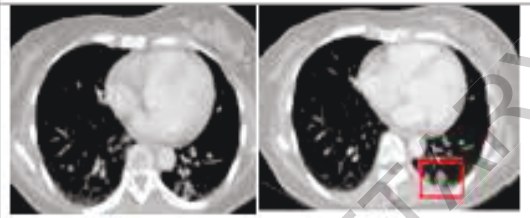
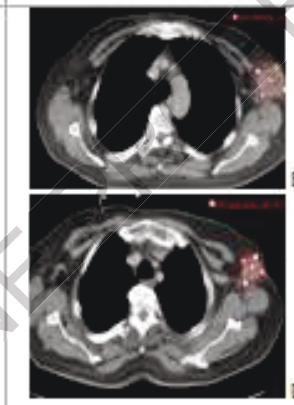
Standard RECIST 1.1	Images	Guidance
Non-Target Lesions at DLE2 **Note:** Unequivocal progression in NT lesions should be selected only in instances where the disease burden has increased to the level where the study drug should be discontinued, even in the presence of stable disease or a partial response in the TLs.	 BL DLE2	Evaluate NTs qualitatively
New Lesions at DLE2 At date of lesion evaluation 2...are new lesions present? • May include a lesion in an anatomical location that was not scanned at baseline (i.e. brain) • Should be unequivocal and not due to differences in scanning technique • If equivocal, assess at next timepoint; if present, PD is the date the lesion was first seen (not the date confirmed)	 BL DLE2	There is no minimum size criteria to identify a new lesion -use clinical judgment
Evaluating Response: Partial Response (PR) • Response is always compared to BL. • If the sum of the diameters (SOD) of TLs decreases by ≥ 30 % compared to BL and there are no new lesions, and no progression of non- target disease, it is a PR. • Confirm ≥ 4 weeks later	 BL DLE2	Record the decreased size of the TL, report response

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

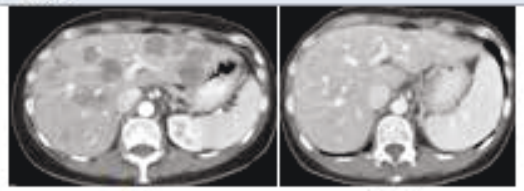
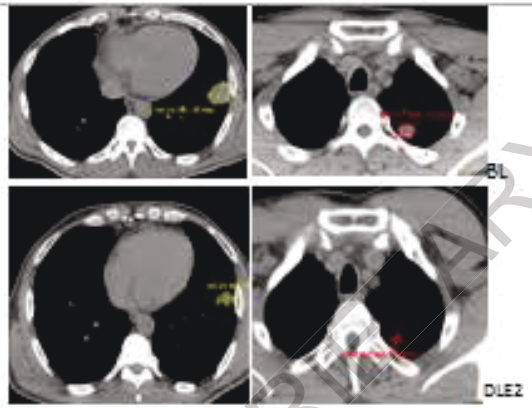
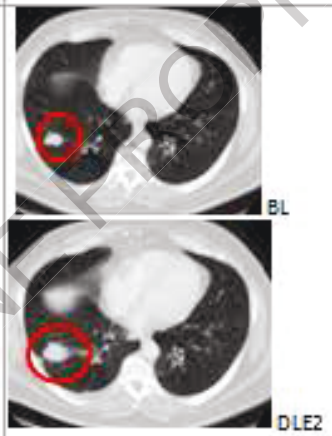
Standard RECIST 1.1	Images	Guidance
Evaluating Response: Complete Response (CR) • Compare to Baseline • If all of the TLs and NTs **completely disappear** and there are no new lesions , report response as CR • Confirm ≥ 4 weeks later		**Note** - if lymph node is the only remaining target disease and it is < 10mm in short axis, a CR is possible with existing measurements.
Evaluating Response: Stable Disease (SD) If the sum of the TLs and the status of the non-target lesions do not reach the criteria to meet PR or PD (increase ≥20% compared to nadir†) the response is SD (**SD = neither 30% decrease compared to BL nor 20% increase compared to nadir**).		SOD = sum of longest diameters (non-nodal) and short axis (nodal) of all TL **Note:** SOD is not reported to [redacted] by the sites In this example, TL size decreases by 28.3%
Evaluating Response: Progressive Disease (PD) If the SOD increases by ≥20% + a 5mm absolute increase compared to nadir, response =PD		SOD = sum of longest diameters (non-nodal) and short axis (nodal) of all TL **Note:** SOD is not reported to [redacted] by the sites In this example, TL size increases by ≥20% compared to nadir

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

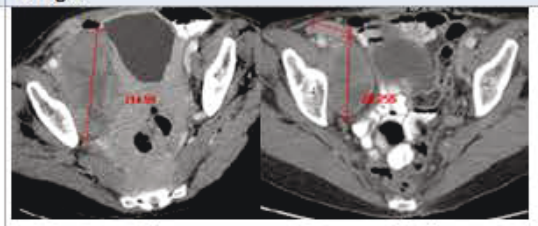
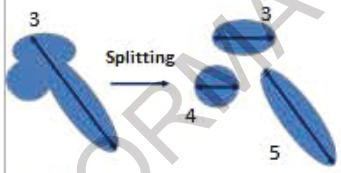
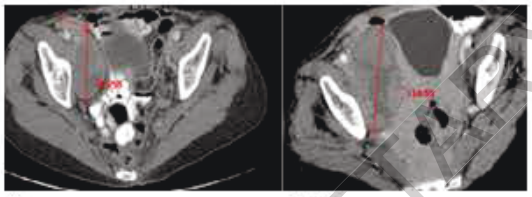
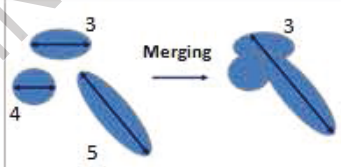
Standard RECIST 1.1	Images	Guidance
Special Cases: **Measuring lesions that split at follow up**	 BL DLE2	 **Splitting** If a TL separates, measure the longest diameter of each resulting lesion separately.
Special Cases: Measuring lesions that merge at follow up	 BL DLE2	 4 = 0 mm **Merging** If initially separate lesions coalesce, record the resulting longest diameter (or short axis for two target lymph nodes) for one of the original TLs and zero mm measurements for the other TL(s).
Special Cases: Lesion Recurrence In subjects with SD or PR, when a lesion disappears and then reappears, it should continue to be measured and added to the (SOD).	No Image	Exception: In subjects with CR, the recurrence of a lesion is PD SOD = sum of longest diameters (non-nodal) and short axis (nodal) of all TL **Note:** SOD is not reported to by the sites

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

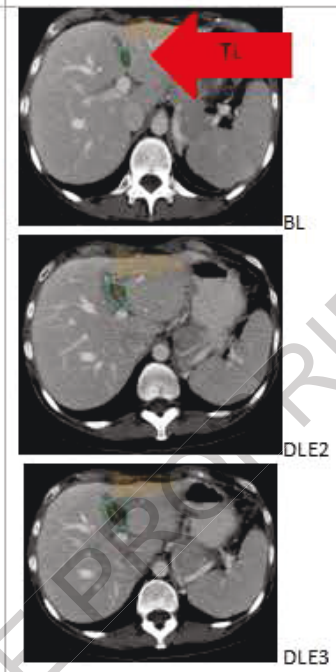
<table>
<tr><th>irRECIST</th><th>Images</th><th>Guidance</th></tr>
<tr><td>▪ After PD is identified at any DLE, a subject may continue treatment if clinically stable, at the discretion of the site PI
▪ Obtain repeat imaging ≥4 weeks later to confirm PD
▪ If PD is not confirmed, treatment can continue
*Note: If PD is confirmed and the subject is experiencing an extraordinary clinical benefit, contact Sponsor to discuss continuing treatment, if noted in clinical protocol.</td><td>No Image</td><td>Clinical Stability per protocol includes:
▪ No symptoms or signs indicating clinically significant PD including labs
▪ No decline in ECOG status
▪ No rapid PD requiring urgent medical intervention

Sites must consult w/sponsor to document clinical stability</td></tr>
<tr><td>PD IS CONFIRMED per irRECIST if:

irRECIST Example 1:

If initial PD is due to increase in tumor burden ≥ 20% + 5 mm absolute increase compared to nadir, PD is Confirmed if tumor burden remains ≥ 20% compared to nadir at follow-up scan.

General Rule: If initial PD is due to increase in tumor burden ≥ 20% + 5mm absolute increase compared to nadir, PD is Confirmed at follow up DLE if ANY of the following are met:

▪ <u>At follow-up scan tumor burden remains ≥ 20% + 5mm absolute increase compared to nadir (Example 1)</u>
▪ New unequivocal PD of non target (qualitative) since last evaluation
▪ One or more new lesion(s) since last evaluation
▪ Note: SOD is not reported to</td><td>Example 1
 
</td><td><table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>25</td><td>nadir</td></tr>
<tr><td>DLE2</td><td>30</td><td>+20% (30-25/25=20)</td></tr>
<tr><td>DLE3</td><td>34</td><td>+36% (34-25/25=36)</td></tr>
</table>
BL-TL liver lesion

DLE2-TL ≥20% compared to nadir (initial PD). TX may continue if clinically stable, repeat scan ≥ 4 weeks.

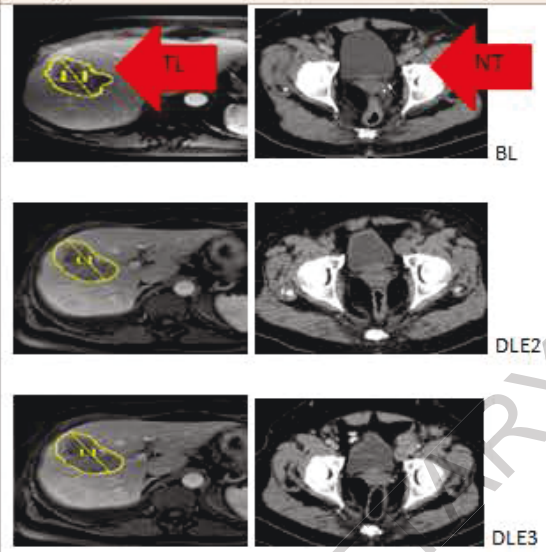
DLE3-confirmatory scan, 4 weeks later, TL remains ≥20% compared to nadir
PD is confirmed</td></tr>
</table>

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

<table>
<tr><th>irRECIST</th><th>Images</th><th>Guidance</th></tr>
<tr>
<td>
irRECIST Example 2:

If initial PD is due to unequivocal progression of NT disease, PD is confirmed from continued unequivocal progression of NT disease.

General Rule: If initial PD is due to unequivocal PD of NT, PD is CONFIRMED at follow up DLE if ANY of the following conditions are met:

▪ <u>NT disease resulting in initial PD is worse (qualitative) (Example 2)</u>
▪ New additional unequivocal PD of NT (qualitative) since last evaluation
▪ Additional new lesion (s) since last evaluation
▪ New PD due to tumor burden (SOD) ≥ 20% + 5 mm absolute increase compared to nadir
▪ Note: SOD is not reported to
</td>
<td>


Example 2
</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>67</td><td>nadir</td></tr>
<tr><td>DLE2</td><td>76</td><td>+13% (76-67/67=13)</td></tr>
<tr><td>DLE3</td><td>77</td><td>+15% (77-67/67=15)</td></tr>
</table>
BL- TL =liver and NT= left inguinal lymph nodes

DLE2- TL is slightly bigger (↑ 13%) but NT nodes have unequivocally progressed (initial PD, due to NT)
TX may continue if clinically stable

DLE3- (confirmatory scan, 4 weeks later), TL is slightly bigger (↑ 15%) but NT nodes continue to unequivocally progress since last evaluation
PD is confirmed
</td>
</tr>
<tr>
<td>
irRECIST Example 3:

PD is confirmed due to worsening of new lesion that was cause for initial PD on repeat scan.

General Rule: If PD is due to New Lesion, PD is CONFIRMED at follow up DLE if ANY of the following conditions are met:

▪ <u>New lesion resulting in initial PD is worse (qualitative) (Example 3)</u>
▪ Additional new lesion (s) since last evaluation
▪ New unequivocal PD of non target (qualitative) since last DLE
▪ New PD due to tumor burden (SOD) ≥ 20% + 5mm absolute increase compared to nadir
</td>
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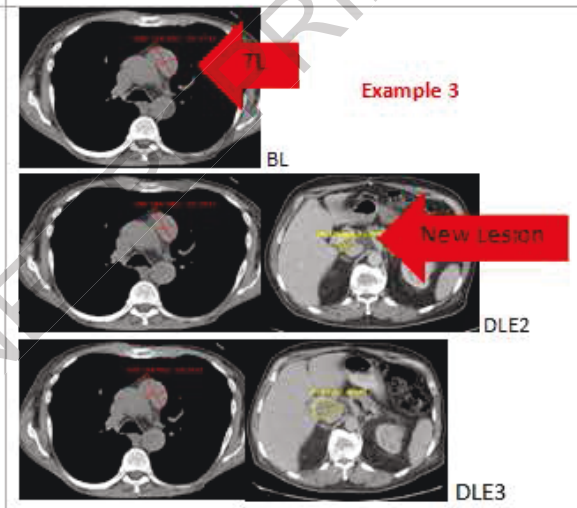


Example 3
</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>30</td><td></td></tr>
<tr><td>DLE2</td><td>30</td><td>0%</td></tr>
<tr><td>DLE3</td><td>30</td><td>0 %</td></tr>
</table>
BL- TL is periaortic lymph node

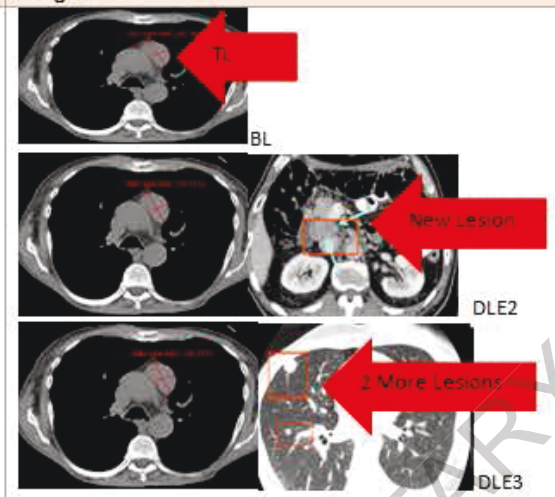
DLE2- TL is unchanged but new lesion (retroperitoneal) is seen =initial PD
TX may continue, if clinically stable, repeat scan in ≥ 4 weeks.

DLE3- (confirmatory scan, 4 weeks later)- TL is unchanged but new lesion from DLE2 worsens
PD is confirmed
</td>
</tr>
</table>

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

<table>
<tr><th>irRECIST</th><th>Images</th><th>Guidance</th></tr>
<tr>
<td>
irRECIST Example 4:

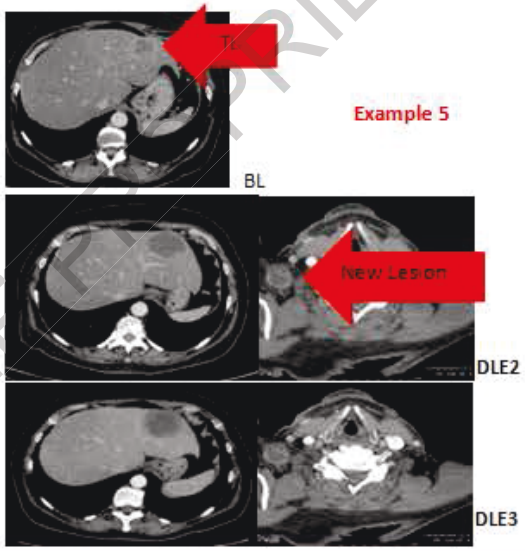
If initial PD is due to new lesion, PD is confirmed due to additional new lesion(s) on repeat scan.

General Rule: If PD is due to New Lesion, PD is CONFIRMED at follow up DLE if ANY of the following are met:
▪ New lesion resulting in initial PD is worse (qualitative) since last evaluation
▪ <u>Additional new lesion (s) since last evaluation (Example 4)</u>
▪ New unequivocal PD of NT (qualitative) since last evaluation
▪ PD due to tumor burden (SOD) ≥ 20% + 5mm absolute increase compared to nadir
▪ Note: SOD is not reported to
</td>
<td>


Example 4
</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>30</td><td></td></tr>
<tr><td>DLE2</td><td>30</td><td>0%</td></tr>
<tr><td>DLE3</td><td>30</td><td>0%</td></tr>
</table>
BL- TL is periaortic (PA) lesion

DLE2- TL is unchanged but new lesion (retroperitoneal) is seen =initial PD)
Continue TX if clinically stable, repeat scan in ≥ 4 weeks.

DLE3- 4 weeks later, confirmatory scan, TL and lesion from DLE2 are both stable, but two additional lesions are seen
PD is confirmed
</td>
</tr>
<tr>
<td>
irRECIST Example 5:
Initial PD is due to new lesion but remains stable at follow up; PD is confirmed due to ≥ 20% increase in tumor burden and 5 mm absolute increase compared to nadir even with stable new lesion

General rule: If initial PD is due to a New Lesion, PD is CONFIRMED at follow up DLE if ANY of the following conditions are met:
▪ New lesion resulting in initial PD is worse (qualitative) since last evaluation
▪ Additional new lesion (s) since last evaluation
▪ New unequivocal PD of non target (qualitative) since last evaluation
▪ <u>New PD due to tumor burden (SOD) ≥ 20% compared to nadir and 5 mm absolute increase (Example 5)</u>
▪ SOD is not reported to
</td>
<td>


Example 5
</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>28</td><td>nadir</td></tr>
<tr><td>DLE2</td><td>45</td><td>+61%</td></tr>
<tr><td>DLE3</td><td>50</td><td>+78 %</td></tr>
</table>
BL- TL in liver
DLE2- BL TL is ≥ 20% compared to nadir + new lesion (neck) =initial PD due to increase in TL tumor burden and new lesion
Continue TX if clinically stable and repeat scan in ≥ 4 weeks.
DLE3- (confirmatory scan, 4 weeks later), New lesion from DLE2= stable, BL TL continues to worsen

PD is confirmed
</td>
</tr>
</table>

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

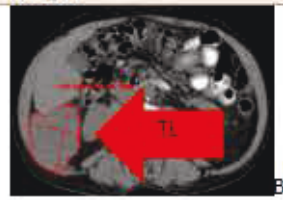
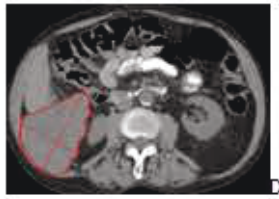
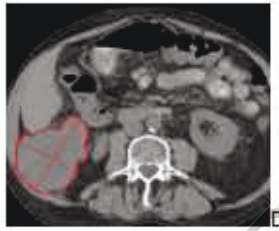
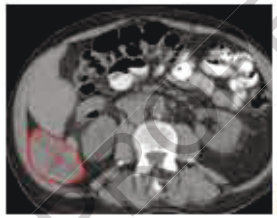
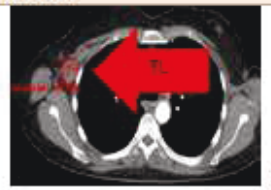
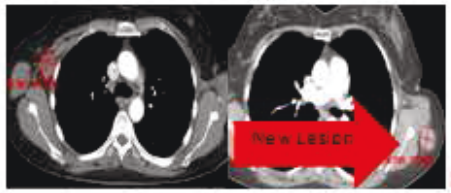
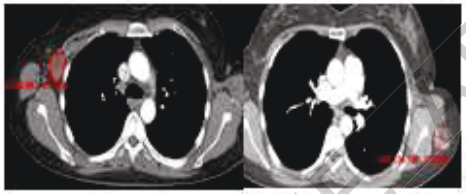
irRECIST	Images	Guidance
irRECIST Example 6: If initial PD is due to increase in tumor burden, PD is not confirmed at follow up DLE if tumor burden is <20% compared to nadir. **General Rule**: If PD is due to increase in tumor burden by ≥20% compared to nadir, PD is NOT CONFIRMED at follow up if **ALL** of the following conditions are met: ▪ **Tumor burden is < 20% compared to nadir** ▪ No unequivocal PD of NT(s) (qualitative) since last evaluation ▪ No new lesion(s) since last evaluation ▪ Continued clinical stability	 BL  DLE2  DLE3  DLE4 **Example 6**	DLE / SOD mm / % change from nadir BL / 20 / nadir DLE2 / 25 / +25% DLE3 / 22 / +10% DLE4 / 15 / -25% BL- TL, large RP mass that meets measurability criteria DLE2- TL increase ≥ 20% compared to nadir =**initial PD** Continue to treat if clinically stable, repeat scan ≥ 4 weeks. DLE3- 4 weeks later, TL continues to decrease, subject = clinically stable, so continue treatment. Shift to regular imaging frequency. **PD not confirmed** DLE4- new nadir, TL continues to decrease, ≥ 30% compared to baseline, achieving a PR Subject may continue to until EOT

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

irRECIST	Images	Guidance
irRECIST Example 7: If initial PD was due to new lesion, PD is NOT confirmed if that new lesion is stable and there is < 20% increase in tumor burden. **General Rule**: If PD is due to New Lesion(s) , PD is NOT CONFIRMED at follow up DLE if **ALL** of the following conditions are met: ▪ **Previous new lesion (that was initially called PD) is not worse (qualitative)** ▪ No additional new lesion(s) since last evaluation ▪ No unequivocal PD of NT(s) (qualitative) since last evaluation ▪ No new PD due to tumor burden (SOD)< 20% compared to nadir) ▪ Continued clinical stability	 BL  DLE2  DLE3 **Example 7**	DLE 2- TL =SD but new lesion in the SQ is seen **(initial PD)**. If clinically stable, continue TX DLE 3- (confirmatory scan, 4 weeks later)- TL and new lesion which caused intial PD are stable Continue TX -**PD unconfirmed** Imaging to follow regular schedule

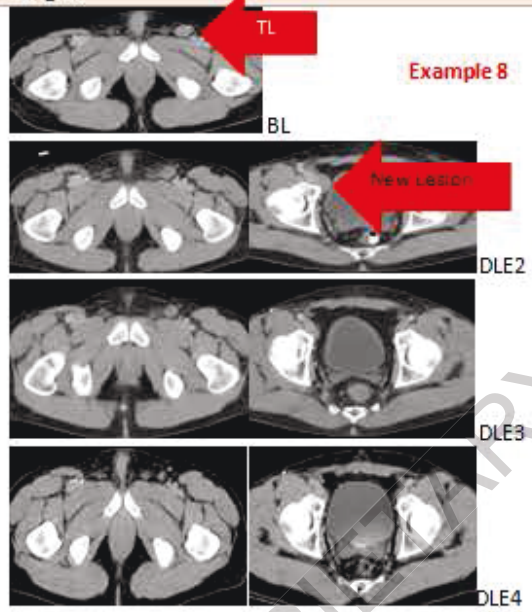
DLE	SOD mm	% change from nadir
BL-DLE1	28	
DLE2	28	0%
DLE3	28	0%

BL-TL (CW)

Table 11: Imaging Guidance for Standard RECIST 1.1 and Immune-related (ir) RECIST (Continued)

<table>
<tr><th>irRECIST</th><th>Images</th><th>Guidance</th></tr>
<tr>
<td>
irRECIST Example 8:
If initial PD is due to new lesion, PD is NOT confirmed if that new lesion is improved at follow up.

General Rule: If PD is due to New Lesion(s) , PD is NOT CONFIRMED at follow up DLE if ALL of the following conditions are met:

▪ <u>Previously new lesion (that was initially called PD) is not worse (qualitative)</u>
▪ No additional new lesion(s) since last evaluation
▪ No unequivocal PD of NT(s) (qualitative) since last evaluation
▪ No new PD due to tumor burden (e.g. SOD< 20%) compared to nadir
▪ Continued clinical stability
▪ SOD is not reported to
</td>
<td>


</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL-DLE2</td><td>21</td><td></td></tr>
<tr><td>DLE3</td><td>21</td><td>0%</td></tr>
<tr><td>DLE4</td><td>21</td><td>0%</td></tr>
<tr><td>DLE5</td><td>13</td><td>-38%</td></tr>
</table>
BL- TL is left inguinal node
DLE2- TL is stable but there is a new right pelvic node=PD by RECIST 1.1

DLE3- TL is stable, new lesion, right pelvic node is resolved; so =SD Continue TX
PD unconfirmed

DLE4- 4 weeks later, TL decreases 38%, no new lesions= PR
DLE 5 , new nadir, now until EOT
Imaging to follow regular schedule
</td>
</tr>
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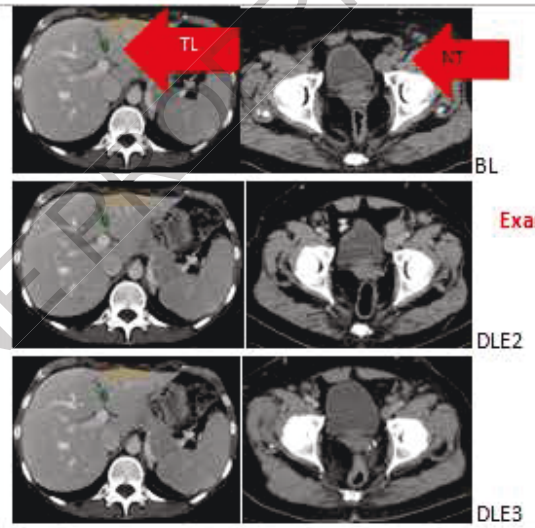
irRECIST Example 9:
If initial PD is due to unequivocal progression of Non-Target disease, PD is NOT confirmed at follow-up DLE if non-target disease is stable or improved General Rule: If PD is due to unequivocal PD of non target, PD is NOT CONFIRMED at follow up DLE if ALL of the following conditions are met:

▪ <u>Initial PD of non target disease is not worse (qualitative)</u>
▪ No additional new unequivocal PD of non target (qualitative) since last evaluation
▪ No new lesion(s) since last evaluation
▪ No new PD due to tumor burden (e.g. SOD< 20%) compared to nadir
▪ Continued clinical stability
</td>
<td>


</td>
<td>
<table>
<tr><th>DLE</th><th>SOD mm</th><th>% change from nadir</th></tr>
<tr><td>BL</td><td>25</td><td></td></tr>
<tr><td>DLE2</td><td>25</td><td>0%</td></tr>
<tr><td>DLE3</td><td>25</td><td>0%</td></tr>
</table>
BL- TL in liver and NT in inguinal lymph nodes
DLE2- TL =SD but NT disease has unequivocally progressed =initial PD

DLE3-TL =SD , NT Lesions are improving
Continue TX

PD unconfirmed

Imaging to follow regular schedule.
</td>
</tr>
</table>

19.3. Appendix C: Table of Abbreviations

Table 12: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AIM	Azacitidine-induced immune
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase (SGPT)
ALK	Anaplastic lymphoma kinase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
AZA	Azacitidine
β-hCG	Beta-subunit of human chorionic gonadotropin
BCG	Bacillus Calmette-Guerin
BLQ	Below the limit of quantitation
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CL/F	Apparent total body clearance
C_{max}	Maximum plasma concentration of drug
CMMoL	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography

Table 12: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DIC	Disseminated Intravascular Coagulation
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DNMT1	DNA methyltransferase-1
DNMTi	DNA methyltransferase inhibitor
DMC	Data Monitoring Committee
EBUS	Endobronchial ultrasound
EC	Ethics Committee
ECI	Events of clinical interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
EOT	End of treatment
EU	European Union
FFPE	Formalin fixed paraffin embedded
FAB	French American British
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
GI	Gastrointestinal
GITR	Glucocorticoid-induced tumor necrosis factor receptor
HBV	Hepatitis B virus

Table 12: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBsAb	Hepatitis B surface antibody
HCl	Hydrochloride
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
HR	Hazard ratio
HUS	Haemolytic Uraemic Syndrome
ICF	Informed consent form
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IDO	Indoleamine 2,3-dioxygenase
ILD	Interstitial lung disease
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
irAEs	Immune-related adverse events
irDCR	Immune-related disease control rate
irPFS	Immune-related progression-free survival
irRC	Immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
irORR	Immune-related overall response rate
IRT	Interactive response technology
ITT	Intent-to-treat

Table 12: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ITP	Idiopathic (or immune) Thrombocytopenia Purpura
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PE	Physical examination
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
RBC	Red blood cell count
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Table 12: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SC	Subcutaneous
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TKI	Tyrosine kinase inhibitor
TIL	Tumor-infiltrating lymphocyte
T_{max}	Time to maximum concentration
TTP	Thrombotic Thrombocytopenic Purpura
$t_{1/2}$	Terminal half-life
ULN	Upper limit of normal
US	United States
Vz/F	Apparent volume of distribution
WBC	White blood cell count
WHO	World Health Organization

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