DISCLOSURE

REDACTED PROTOCOL AMENDMENT 4

CC-486-MDS-006

A PHASE 2, INTERNATIONAL, MULTICENTER, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-486 (ORAL AZACITIDINE) ALONE AND IN COMBINATION WITH DURVALUMAB (MEDI4736) IN SUBJECTS WITH MYELODYSPLASTIC SYNDROMES WHO FAIL TO ACHIEVE AN OBJECTIVE RESPONSE TO TREATMENT WITH AZACITIDINE FOR INJECTION OR DECITABINE

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A PHASE 2, INTERNATIONAL, MULTICENTER, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-486 (ORAL AZACITIDINE) ALONE AND IN COMBINATION WITH DURVALUMAB (MEDI4736) IN SUBJECTS WITH MYELODYSPLASTIC SYNDROMES WHO FAIL TO ACHIEVE AN OBJECTIVE RESPONSE TO TREATMENT WITH AZACITIDINE FOR INJECTION OR DECITABINE

INVESTIGATIONAL PRODUCT (IP):	CC-486 (oral azacitidine) Durvalumab (MEDI4736)
PROTOCOL NUMBER:	CC-486-MDS-006
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Back-up 24 Hour Global Emergency Contact Call Center: PPD

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{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
PPD	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

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Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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PROTOCOL SUMMARY

Study Title

A Phase 2, International, Multicenter, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy and Safety of CC-486 (oral azacitidine) Alone and in Combination With Durvalumab (MEDI4736) in Subjects With Myelodysplastic Syndromes Who Fail to Achieve an Objective Response to Treatment With Azacitidine for Injection or Decitabine

Indication

The treatment of myelodysplastic syndromes (MDS) not responding to prior treatment with azacitidine for injection or decitabine.

Objectives

Primary Objective

The primary objective of this study is to investigate the efficacy of CC-486 as monotherapy, and in combination with anti-PD-L1 monoclonal antibody, durvalumab (MEDI4736), in subjects with MDS that did not respond to treatment with an injectable hypomethylating agent (HMA – azacitidine for injection or decitabine), or were unable to tolerate treatment with an injectable HMA.

Secondary Objectives

- Assess the safety and tolerability of CC-486 alone and in combination with durvalumab, as treatment for MDS
- Describe the clinical relevance of objective hematologic and/or biologic responses associated with treatment with CC-486 alone and in combination with durvalumab
- Evaluate the impact (if any) of durvalumab on the pharmacokinetics of CC-486 and CC-486 on durvalumab in subjects with MDS

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Study Design

This is a Phase 2, international, multicenter, randomized, parallel group, open-label study consisting of: *Screening, Safety run-in, Randomized Treatment*, *Follow-up*, and *Extension Phase*. The randomized portion of the study will be preceded by a non-randomized safety run-in to

evaluate the safety and tolerability of the planned regimens, and to determine the recommended dose for the monotherapy and combination therapy arms for the randomized phase.

The safety run-in will utilize a 3+3 design to include at least 3 subjects treated with monotherapy at the dose and schedule expected to be used in combination, as well as at least 3 subjects treated with combination therapy to evaluate safety and tolerability. The monotherapy arm will be enrolled first to confirm the expected safety profile of CC-486 alone at the planned dose and schedule in the target population.

Data from the safety run-in will be reviewed in conjunction with the study investigators, Scientific Steering Committee, and Data Monitoring Committee to ensure agreement with the recommended Phase 2 dosing regimens prior to beginning enrollment to the randomized treatment phase.

The randomized treatment phase will be conducted in 2 stages, with a futility assessment planned at the completion of Stage 1 to determine whether the null hypothesis *(H_0: $p < 12.5\%$)* can be rejected with 3 or more responses in Stage 1. If 3 or more responses have been observed before the end of Stage 1, the planned futility assessment may be performed earlier than at the completion of Stage 1 to confirm the finding of responses. This earlier analysis will replace the futility analysis planned at the completion of Stage 1. This earlier futility assessment will have the same integrity as the futility assessment planned at the completion of Stage 1. An analysis will be performed at the completion of Stage 2 to estimate the overall response rate of treatment of all the subjects in the cohort. All subjects who receive investigational product (IP) in this study will continue to be followed for information related to post-treatment safety and subsequent MDS therapies, as described in Section 4.1.5.

Approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected study centers will participate in PK sampling procedures as described in Section 6.10.

Extension Phase

At the Investigator's discretion and following confirmation of eligibility criteria below, subjects can enter the Extension Phase (EP):

Eligibility Criteria:

- Subjects who have signed the informed consent for the EP of the study;
- Subjects receiving oral azacitidine and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral azacitidine in the EP;
- Subjects who do not meet any of the criteria for study discontinuation (see Section 12).

Details for the EP are provided in Appendix J.

The study design is described in detail in Section 4.1.

Study Population

The study will enroll at least 70 to 194 evaluable subjects with MDS who did not respond to an adequate course of therapy with an injectable hypomethylating agent (iHMA – azacitidine for injection or decitabine) as their last treatment for MDS, or who were unable to tolerate an iHMA

following at least 3 months of attempted treatment. Complete inclusion and exclusion criteria for this study, including the definition of an *adequate course of therapy,* and required parameters for hematology, performance status, renal and hepatic function are detailed in Section 7.

At least 3 subjects will be enrolled in each of two treatment groups (monotherapy and combination therapy) during the safety run-in phase of the study: The monotherapy treatment group will be enrolled first and evaluated for dose-limiting toxicity (Section 4.1.2.1), prior to selecting a CC-486 dose and regimen, and initiating enrollment for the combination treatment group. Progressive disease (PD) and stable disease (SD) designations are made based on the subject's best response to iHMA therapy determined at the start of the study (see Section 4.1).

A total number of 64 evaluable subjects will be enrolled equally during the first stage of the randomized treatment phase into 4 cohorts: SD monotherapy, PD monotherapy, SD combination therapy, and PD combination therapy. If the required number of objective responses are observed in a cohort, the cohort will be continued into the second stage of study to include 25 more subjects (see Section 4.1, Section 10.3, and Figure 2).

The study is closed to further enrollment with the last subject enrolled in June 2018. A total of 65 subjects were enrolled in the study. At the time of this amendment, 6 subjects are ongoing in the Monotherapy SD/PD cohorts (One subject from Phase 1, and 5 from Phase 2).

Length of Study

The total duration of this study is expected to be approximately 75 months (see Section 4.3).

Subjects will undergo screening procedures over a period of up to 28 days following the signing of their informed consent document (ICD). Eligible subjects will continue to the safety run-in or the randomized treatment phase of the study where they will receive IP for up to six 28-day treatment cycles. Those who derive benefit from the treatment may continue IP until loss of that benefit (Section 4.1.3).

After treatment discontinuation, subjects will be followed for 28 days for CC-486 safety-related issues and 90 days for durvalumab safety-related issues. After that, subjects will be contacted by telephone every 3 months in the follow-up phase of the study.

The enrollment period for this study is expected to last approximately 39 months. The treatment and follow-up periods are expected to conclude approximately 12 months after the last subject is enrolled. The Extension Phase is expected to last approximately 24 months. Therefore, the total duration of the study is expected to be approximately 75 months.

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

The study will conclude once all subjects have completed or discontinued from the Extension Phase.

Study Treatment (Investigational Product – IP)

CC-486 (Oral Azacitidine)

Eligible subjects who are assigned to the monotherapy treatment arm will receive CC-486 at the dose and schedule identified during the safety run-in phase of the study. Dose and schedule may be reduced to manage toxicity or increased as described in Section 8.2. Subjects can continue treatment with CC-486 as long as all protocol-specified re-treatment criteria continue to be met (see Section 8.2.5).

Durvalumab (MEDI4736)

Eligible subjects who are assigned to the combination therapy treatment arm will receive CC-486 as described above, and durvalumab 1500 mg on Day 1 of each 28-day treatment cycle by 1-hour (± 5 minutes) intravenous (IV) infusion. For toxicity considered by the investigator to be related to treatment with durvalumab, including immune-mediated adverse events (imAEs) or infusion-type reactions, the infusion of durvalumab may be slowed, interrupted, or discontinued as described in Section 8.2.4.2. Dose reduction for durvalumab is not permitted. Subjects can continue treatment with durvalumab in combination with CC-486 as long as all protocol-specified re-treatment criteria continue to be met (see Section 8.2.5).

Overview of Efficacy Assessments

The primary efficacy endpoint of this trial is the proportion of subjects achieving an objective response (hematologic improvement (HI), partial remission (PR), complete remission (CR), or marrow CR – modified from International Working Group (IWG) 2006 criteria – Appendix F) to treatment with CC-486 alone and in combination with durvalumab. To assess this endpoint, bone marrow examination will be required prior to beginning IP and following every 2 cycles of treatment during the first 6 treatment cycles. Subjects who continue beyond Cycle 6 will undergo bone marrow examination following every 3 treatment cycles or when necessary to confirm suspected hematologic response or disease progression. Bone marrow samples (aspirate and/or biopsy), along with a peripheral blood smear and pertinent clinical information will be submitted for review by an independent pathologist to provide consistency in determinations of disease classification, response, and/or progression.

Hematologic parameters including complete blood count (CBC) with white blood cell (WBC) differential and platelets will be assessed by the central laboratory at the frequency described in the Table of Events (Table 2) and Section 6.7.7.

To understand the potential impact of any immunogenic response to durvalumab on the efficacy of the treatment, immunogenicity assessment will be performed at the frequency described in the Table of Events (Table 2).

Overview of Safety Assessments

- Adverse events (AEs) including adverse events of special interest (AESIs) (please refer to the Durvalumab Investigator's Brochure; Section 5.4.2 Summary of Risks).
- physical examination
- vital signs and body weight measurement
- Eastern Cooperative Oncology Group (ECOG) performance status
- hematology (CBC with differential and platelets)
- coagulation parameters

- serum chemistry (to include amylase and lipase) and thyroid function tests
- concomitant medications, therapies, and procedures
- pregnancy testing (for females of childbearing potential [FCBP] only)
- electrocardiogram
- urinalysis

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Overview of Pharmacokinetics Assessments

Blood samples for pharmacokinetic analysis will be collected from approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected sites. This will enable assessment of drug-drug interactions. Subjects participating in PK procedures will agree to have blood samples collected as described in Section 6.10.

Sample Size Determination and Statistical Analysis (Randomized Treatment Phase)

The sample size required will be identical for each cohort and is estimated using the optimal design of the Simon's two-stage design method (Simon, 1989). The null hypothesis of the response rate will be tested against a one-sided alternative.

For each cohort, the null hypothesis of response rate (H0: $p \leq 0.125$) will be tested against the alternative hypothesis of response rate (H1: $p \geq 0.27$) with a type I error rate of 10% and 80% power. During the first stage, 16 subjects will be accrued per cohort. If there are 2 or fewer responses in these 16 subjects, the cohort will be stopped and no further recruitment will be needed. Otherwise, 25 additional subjects will be accrued per cohort for a total of 41 subjects in

each cohort. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected.

For each cohort, in addition to the evaluation of treatment responses based on objective response criteria, the quality of responses will also be considered for the decision whether to continue the cohort to the second stage of the study. Quality of response will be assessed based on the magnitude of hematologic and biologic responses observed in individual subjects, with special consideration for response duration, and will be specified with more details in the final SAP.

For the primary objective, the response rate at the end of Stage 2 and the associated 95% confidence interval will be estimated for each cohort which completes Stage 2. Similar estimates for Stage 1 will be provided for any cohort which does not continue to Stage 2. The response rates at the end of Stage 2 will be compared between cohorts of SD and PD subjects (if both cohorts finished Stage 2) using the relative risk ratio or other appropriate methods. Specifically, if relative risk method is used, the ratio of response rates for both cohorts and the associated 95% confidence interval will be estimated. Description of methodologies will also be provided in the SAP if other methods are used.

For the secondary objectives, Kaplan-Meier's method will be used to analyze the time-to-event variables, which include overall survival, time to response, duration of response, and time to disease progression. The safety and tolerability of the regimen in this sample of subjects will be estimated and the corresponding 95% confidence intervals will be estimated.

An Independent Data Monitoring Committee will review the safety data during the safety run-in phase. The committee will also review the efficacy and safety data during the randomized phase of the study, in addition to the recommendation for any cohort to continue to Stage 2 of the study. The details of the data monitoring plan will be provided in a separate charter document.

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1. INTRODUCTION

1.1. Myelodysplastic Syndromes

Myelodysplastic syndrome (MDS) is an umbrella term that encompasses a heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. MDS is typically characterized by bone marrow hyperplasia and peripheral cytopenias that manifest clinically as anemia, neutropenia, and/or thrombocytopenia of variable frequency and severity, with symptoms of anemia being the most frequently-presenting manifestation. Anemia is the most frequent laboratory finding and it often progresses to red blood cell (RBC) transfusion dependence. Other less common presenting clinical features related to the cytopenias are an increased risk of infection and/or hemorrhage and a potential to progress to acute myeloid leukemia (AML) (Catenacci, 2005). The latter clinical features often appear over time and are associated with more advanced disease.

Myelodysplastic syndromes are classified according to World Health Organization (WHO) criteria by pathologic features on bone marrow examination into the following categories (Brunning, 2008; Vardiman, 2009; Appendix A):

- Refractory cytopenia with unilineage dysplasia (RCUD)
  - refractory anemia (RA)
  - refractory neutropenia (RN)
  - refractory thrombocytopenia (RT)
- Refractory Anemia with ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts-1 (RAEB-1)
- Refractory anemia with excess blasts-2 (RAEB-2)
- Myelodysplastic syndrome -unclassified (MDS-U)
- MDS associated with isolated del(5q)

Or by French-American-British (FAB) classification system subtypes of MDS (Bennett, 1982; Appendix B):

- Refractory anemia (RA)
- Refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions)
- Refractory anemia with excess blasts (RAEB)
- Refractory anemia with excess blasts in transformation (RAEB-T)
- Chronic myelomonocytic leukemia (CMML)

A patient's disease is also assigned to one of 4 prognostic groups (Low, Intermediate-1 [INT-1], Intermediate-2 [INT-2], and High risk) according to the International Prognostic Scoring System (IPSS - Appendix C) based on cytogenetic features, number of cytopenias, and bone marrow

blast percentages. Overall survival and risk of progression to AML is significantly different in the 4 risk groups. Median survival for patients in these risk groups being 5.7 years (Low), 3.5 years (INT-1), 1.2 years (INT-2), and 0.4 years (High). The median time for 25% of patients to progress to AML is 9.4, 3.3, 1.1, and 0.2 years, respectively (Greenberg, 1997).

Allogeneic bone marrow transplantation has been effective, both in patients under the age of 50 years and in those older than 50 years who are in good health and who have suitable human leukocyte antigen (HLA) matched donors. However, this approach has limited value, since most patients with MDS are older than 65 years of age and have significant comorbidities that preclude the use of this modality as it is associated with a high morbidity and mortality rate, as described in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines: MDS (NCCN, 2015).

For patients diagnosed with, or progressing to, higher-risk disease, the standard of care is treatment with a locally-available injectable HMA: azacitidine for injection or decitabine. Injectable HMAs can produce hematologic response or improvement in approximately half of treated patients, but responses are transient and responding disease will eventually relapse (Grinblatt, 2008; Lyons, 2009; Musto, 2010; Silverman, 2002).

There are no approved (or proven) treatment options following failure of treatment with an injectable HMA. The mainstay of therapy in this setting among patients not eligible for autologous stem cell transplant remains supportive care, including RBC and/or platelet transfusions, treatment of infections, and the use of erythropoiesis stimulating agents (ESAs) such as epoetin alfa or darbepoetin, plus hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) when needed (Lübbert, 2000; NCCN, 2015; Kadia, 2011). Neither ESAs nor myeloid growth factors are approved for the treatment of MDS.

Thus, additional data regarding the use of potentially-effective agents in this population is greatly needed.

1.2. CC-486 (Azacitidine)

CC-486 is an oral formulation of azacitidine. Azacitidine is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. In the United States (US), azacitidine (Vidaza®) is approved for the treatment of all 5 FAB classification subtypes of MDS: RA, RARS, RAEB, RAEB-T, and CMML, but it is not routinely utilized in the lower-risk disease setting. Azacitidine is approved in the European Union (EU) for the treatment of adult non-hematopoietic stem cell transplantation-eligible patients with IPSS INT-2 or high-risk MDS, CMML with 10% to 29% marrow blasts without myeloproliferative disorder, and AML with 20% to 30% blasts and multi-lineage dysplasia, according to the WHO classification. In addition to the US and EU, azacitidine is currently approved in 30 other countries, including Canada, Switzerland, Australia, and Japan, for the treatment of MDS (approvals for specific subtypes vary by country). Current approved routes of administration include subcutaneous and intravenous (approvals vary by country). Similarly, decitabine (Dacogen®), another hypomethylating agent, is approved in the US for treatment of all FAB classification subtypes and IPSS INT-1, INT-2 and high-risk MDS.

Azacitidine has strong in vitro and in vivo anti-leukemic activity and the ability to induce differentiation at lower concentrations in hematopoietic and non-hematopoietic cell lines. The

effects of azacitidine may result from multiple mechanisms, including inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation can be attributed to its activity as a hypomethylating agent. The degree of methylation of cytosine residues in DNA has been demonstrated to play a role in gene expression. Indeed, hypermethylation of cytosine residues of genes critical to ensure orderly cell proliferation and maturation (differentiation) is frequently found in primary neoplasms and tumor cell lines (Zingg, 1997). Therefore, use of an inhibitor of DNA methylation, such as azacitidine, is a rational approach to reversing these epigenetic aberrations in the malignant clone and to re-establishing antiproliferative signals that were extinguished by hypermethylation. Preliminary data from the AZA-PH-GL-2003-CL-001 survival study (Herman, 2009) with azacitidine in higher-risk MDS patients found, from analysis of pretreatment bone marrow methylation density, that the overall survival benefit observed with azacitidine versus conventional care regimens (CCR) was independent of the methylation status of the 5 genes analyzed (CDKN2B [p15], SOCS1, CDH1 [E-cadherin], TP73, and CTNNA1 [α-catenin]). However, increasing methylation was associated with worse overall survival. Patients with lower levels of methylation treated with azacitidine had the best overall survival, suggesting that they may derive greater benefit from azacitidine.

Azacitidine has been studied extensively in MDS and has been shown in a large, randomized, Phase 3 trial of higher-risk MDS patients to provide a survival advantage of 9.4 months over CCR. The median overall survival of azacitidine-treated patients was 24.5 months compared with 15.0 months for the CCR group, which included best supportive care, low-dose cytarabine, or intensive chemotherapy (Fenaux, 2009). The clinical experience with azacitidine in AML is smaller, but positive efficacy results have been obtained. In a subset of 113 patients with WHO-defined AML (mean age 70 years, 24% with unfavorable karyotype, median bone marrow blasts 23%) from the larger MDS study discussed above, the median overall survival was 24.5 months (n = 55) in the azacitidine arm compared with 16.0 months (n = 58) in the CCR arm (Fenaux, 2008). Additionally, the outcome was not significantly different in patients with an unfavorable karyotype, although the sample size was small. Silverman et al, using WHO-defined AML criteria for diagnosis, reported a median overall survival of 19.3 months (n = 27) in patients treated with azacitidine compared with 12.9 months (n = 25) in patients who received best supportive care (Silverman, 2006). Additionally, Goldberg et al. reported on 33 patients who received azacitidine (n = 11, median age 74) or 7+3 intensive chemotherapy (n = 22, median age 67 years) (Goldberg, 2006). Median blast count at baseline was 42% in the azacitidine group and 65% in the intensive chemotherapy group. The median overall survival was 13.2 months in the patients treated with azacitidine compared with 9.2 months in patients receiving intensive chemotherapy (Goldberg, 2006). All of the above-mentioned studies used the standard injectable azacitidine dose of 75 mg/m^2/day for 7 days.

Most responses to azacitidine occur by the completion of 6 cycles of treatment, but responses may still occur beyond this (Musto, 2010; Silverman, 2006). Elderly patients (> 70 years of age) respond as well as younger patients, and failure to respond to prior therapy with ESAs does not preclude possible responses to azacitidine (Musto, 2010). Overall response rates in lower-risk MDS subjects have been reported as approximately 50% in various studies (Grinblatt, 2008; Lyons, 2009; Musto, 2010; Silverman, 2002).

An oral formulation of azacitidine (CC-486) has been evaluated in 3 clinical studies to date. Results from a pilot study (AZA PH US 2007 PK 004) indicated that azacitidine in an oral formulation was bioavailable (Garcia-Manero, 2008). This was confirmed when evaluating several different formulations of the drug in a Phase 1 study (AZA PH US 2008 CL 008). Results from another Phase 1 study of CC-486 in subjects with MDS, CMML, or AML (AZA PH US 2007 CL 005) indicated that administration on different treatment schedules (7-, 14-, and 21-day once daily [QD] and 14- and 21-day twice daily [BID]) was feasible, generally well-tolerated, and exhibited biologic and clinical activity (Garcia-Manero, 2009; Garcia-Manero, 2010).

1.3. Durvalumab (MEDI4736)

Durvalumab is briefly described below. Refer to the current Investigator's Brochure for further details.

Durvalumab is a human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocytes (T-cells) and cluster of differentiation (CD) 80 on immune cells and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

1.3.1. Durvalumab Experience in Solid Tumors

Study CD-ON-MEDI4736-1108 is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, pharmacokinetics (PK), immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists.

As of 12 July 2016, a total of 1012 subjects with advanced solid tumors have been treated in this study. Of these subjects, 970 have received durvalumab at 10 mg/kg once every 2 weeks (Q2W), either in the dose-escalation or dose-expansion phase of the study. The 10 mg/kg Q2W cohort represents combined data from subjects treated with this dosing regimen in either the dose-escalation or dose-expansion phase. The 10 mg/kg Q2W cohort comprises subjects with non-small cell lung cancer (NSCLC) (n = 304), urothelial carcinoma (n = 191), squamous cell carcinoma of the head and neck (SCCHN) and microsatellite instability high (both n = 62), gastro-oesophageal cancer (n = 51), ovarian cancer (n = 47), hepatocellular carcinoma (HCC) and triple-negative breast cancer (TNBC) (both n = 40), pancreatic adenocarcinoma (n = 31), uveal melanoma (n = 24), non-SCCHN human papilloma virus (positive) (HPV+) (n = 22), advanced cutaneous melanoma and small cell lung cancer (both n = 21), glioblastoma multiforme and soft tissue sarcoma (both n = 20) and nasopharyngeal carcinoma (n = 10). Subjects in the 10 mg/kg Q2W dose cohort were exposed to a median of 6 doses of durvalumab, ranging from 1 to 27 doses.

Of the 970 subjects treated with 10 mg/kg Q2W, 947 subjects (97.6%) had at least 1 adverse event (AE) (regardless of causality). AEs (all grades) reported in decreasing order of frequency in ≥10% of subjects were fatigue (37.6%), nausea (23.7%), decreased appetite (23.2%), dyspnea (21.9%), constipation (20.2%), diarrhea and cough (17.9% each), back pain (16.5%), vomiting (15.9%), anemia (15.6%), abdominal pain (14.4%), pyrexia (13.9%), arthralgia (13.1%), edema

peripheral (12.1%), pruritus (11.6%) and headache (11.2%). Across the tumor types, the overall incidence of AEs was generally similar.

Grade 3 or higher AEs were reported in 295 subjects (30.4%) and were manageable by general treatment guidelines described in the toxicity management guidelines contained in each of the study protocols. Events occurring in >2% of subjects were anemia (6.2%), dyspnea (6.0%), hyponatremia (5.4%), fatigue (3.9%), gamma glutamyltransferase (GGT) increased (3.6%), abdominal pain (3.1%), aspartate aminotransferase (AST) increased (2.9%), back pain (2.9%) and dehydration (2.6%).

A total of 554 subjects (57.1%) reported AEs that were considered by the investigator to be related to investigational product. Treatment-related AEs (all grades) reported in > 5% of subjects were fatigue (18.7%), nausea (7.9%), diarrhea (7.6%), pruritus (6.8%), decreased appetite (6.7%), hypothyroidism (6.3%) and rash (6.0%). The majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 88 subjects (9.1%).

Treatment-related ≥ Grade 3 or 4 events reported in ≥ 2 subjects were fatigue (1.6%), AST increased (1.0%), alanine aminotransferase (ALT) increased (0.8%), GGT increased (0.7%), hyponatremia and diarrhea (0.5% each), colitis (0.4%), decreased appetite and vomiting (0.3% each), and alkaline phosphatase (ALP) increased, anemia, arthralgia, autoimmune hepatitis, blood bilirubin increased, dyspnea, hyperglycemia, infusion related reaction, leukopenia, nausea, neutropenia, nervous system disorder, rash maculo-papular, thrombocytopenia, transaminases increased and weight decreased (0.2% each). Four subjects had a treatment-related Grade 5 event (autoimmune hepatitis, immune thrombocytopenic purpura, pneumonia and pneumonitis).

Serious adverse events (SAEs) (regardless of causality) have been reported in 504 of 970 subjects (52.0%) treated with 10 mg/kg durvalumab Q2W. Serious adverse events reported in >1% of subjects by descending order of frequency were: NSCLC (4.5%), dyspnea (4.3%), abdominal pain and bladder cancer (2.7% each), pneumonia (2.5%), pyrexia and sepsis (2.3% each), general physical health deterioration (2.0%), back pain (1.8%), acute kidney injury, dehydration, pleural effusion and urinary tract infection (1.5% each), lung neoplasm malignant (1.4%), respiratory failure and vomiting (1.2%) and hypercalcemia (1.0%). Thirty-nine subjects (4.0%) had SAEs considered by the investigator to be related to durvalumab. Treatment related SAEs that occurred in > 1 subject each were colitis and pneumonitis (4 subjects each), nervous system disorder (3 subjects), and acute kidney injury, AST increased, and diarrhea (2 subjects each). The majority of the treatment-related SAEs were Grade 3 or higher in severity and recovered with or without sequelae.

No clinically meaningful difference in the AE profile across doses was observed, including Grade 3 or 4 events, SAEs, AEs leading to discontinuation, or treatment-related AEs.

As of 29 April 2016, 304 NSCLC subjects had received durvalumab monotherapy; 144 subjects (47%) with non-squamous and 160 subjects (53%) with squamous histology. Subjects with tumors defined as PDL1 positive had improved overall rate of objective response (ORR) and overall survival (OS). The ORR, was 25% and 6% in PD-L1 positive and negative subjects, respectively. The 12-month OS rate was 55.8% and 38.8% in PD-L1 positive and negative subjects, respectively.

As of 29 April 2016, 62 subjects with recurrent/metastatic SCCHN had received durvalumab monotherapy. Among seven responders, six subjects had a DOR for ≥12 months with longest

DOR being 19.8 months. Six and 12-month OS is 62% and 42%, respectively. Urothelial Carcinoma: As of data cut-off (DCO) on 20 November 2015, 61 subjects had been enrolled into the urothelial cell cohort. Forty-two subjects who initiated study therapy ≥ 12 weeks prior to DCO were evaluable for response. Confirmed ORR was 46% in the PD-L1 positive subgroup compared to 0% in the PD-L1 negative subgroup. ORR in the entire response evaluable population was 31% (13/42 subjects).

Other indications: In PD-L1 unselected subjects, the ORR, based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma to 17.4% in advanced cutaneous melanoma, and disease control rate (DCR)-24w ranged from 4.2% in TNBC to 39.1% in advanced cutaneous melanoma. Across the PD-L1 high tumors, ORR was >10% for advanced cutaneous melanoma and HCC (33.3% each). In the PD-L1-positive subset, DCR- 24w was >10% in advanced cutaneous melanoma (66.7%) and HCC (33.3%).

As of 24 July 2016, PK data were available for a total of 977 subjects following treatment with 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W (dose escalation), 10 mg/kg Q2W (dose-expansion), and 20 mg/kg Q4W (dose-exploration) durvalumab administered as an intravenous (IV) infusion over 60 minutes. PK samples were analyzed using an electrochemiluminescence (ECL) method for quantitative determination of durvalumab in human serum with lower limit of quantitation (LLOQ) of 50 ng/mL in 100% matrix.

Following the first IV dose, durvalumab exhibited nonlinear PK at doses < 3 mg/kg Q2W likely due to saturable target-mediated clearance (CL) and exhibited linear PK at doses ≥ 3 mg/kg Q2W. The area under the concentration-time curve (AUC)0-14 increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose-proportionally at doses of < 3 mg/kg, likely due to saturable target-mediated CL. Maximum observed concentration (C_{max}) increased in a dose-proportional manner within the dose range examined. The steady state was achieved at approximately Week 16. Accumulation of durvalumab was observed following repeated dosing. Mean accumulation ratio (AR) ranged from 0.64 to 1.87 and 3.15 to 4.93 for C_{max} and trough concentration (C_{trough}), respectively.

As of 24 July 2016, a total of 790 subjects provided samples for anti-drug antibody (ADA) analysis. Only 25 of 790 subjects (1 subject each in 0.1 and 3 mg/kg cohorts, 17 subjects from 10 mg/kg cohort) were ADA positive. One subject in the 10 mg/kg cohort tested positive for anti-TM antibody. Three subjects were neutralizing ADA (nAb) positive. For the proposed clinical dose, of 751 subjects (ADA evaluable population) treated with 10 mg/kg Q2W, 2.8% (21/751) had treatment-emergent ADAs and 0.1% (1/751) of subjects were positive for nAb. Based on population PK covariate analysis, ADA positive status was not associated with a clinically relevant reduction of exposure to durvalumab. At the 10 mg/kg Q2W dose, sPD-L1 suppression in ADA positive subjects was similar to that observed in ADA negative subjects. The relevance of ADA on safety and efficacy is unknown given the small number of ADA positive subjects.

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1.4. Study Rationale

The original protocol rationale was to evaluate the efficacy and safety of CC-486 as a monotherapy only.

Currently, this clinical study will evaluate the efficacy and safety of CC-486 alone, and in combination with durvalumab, in subjects with myelodysplastic syndromes, refractory to treatment with azacitidine for injection or decitabine; ie, *stable disease* or *disease progression* was the best response to that treatment.

1.4.1. Azacitidine Exposure

While injectable hypomethylating agents (azacitidine for injection and decitabine) remain the standard of care in the treatment of IPSS higher-risk MDS, as many as half of affected patients do not respond to treatment, and nearly all those who do respond will eventually relapse. Upon failure of treatment with azacitidine for injection and/or decitabine, the prognosis for patients

with higher-risk disease is dismal, with median overall survival on the order of 4-6 months (Prebet, 2011; Jabbour, 2010). Similarly, injectable HMAs are approved for treatment of IPSS lower-risk MDS in some countries, and while there are few data to characterize outcomes in lower-risk disease following failure of these agents, prognosis is poor and for patients who are not eligible for allogeneic stem cell transplant, no proven treatment options currently exist (Jabbour, 2013).

Aberrant hypermethylation of DNA is a feature of myelodysplastic syndromes, and is implicated in the pathogenesis and progression of disease (Gore, 2006). This supports the notion that epigenetic changes play an important role in MDS transformation and may be exploited. However, association between the degree of constitutive methylation and magnitude of reduction in methylation state via treatment with HMAs has not been clearly correlated with treatment outcomes (Follo, 2009).

Azacitidine is a cytidine analog that may, in part, exert its antineoplastic effect by incorporation into DNA of cycling cells and subsequent hypomethylation through inhibition of DNA methyltransferases. Optimal drug activity may require an increased window of exposure to malignant cells to increase the opportunity for cycling cells to incorporate drug (Mahfouz, 2013; Stresemann, 2008).

An oral formulation of azacitidine provides an opportunity to deliver the drug daily over a more prolonged schedule than can be practically achieved with parenteral therapy. In a Phase 1 dose-finding study, the safety, bioavailability, and biologic effects of CC-486 were evaluated. Compared with 75 mg/m^2 subcutaneous (SC) AZA, 300 mg CC-486 QD x 14 days and QD x 21 days provided mean cumulative exposures (AUC) per cycle of approximately 38% and 56%, respectively. With SC AZA 75 mg/m^2 QD, 7/28 days, DNA methylation was significantly reduced, with its greatest reduction in global de-methylation score (GDMS – percent of highly-methylated loci) of -8.8% at Day 15. However, methylation increased throughout the remaining 21 days of the cycle to a GDMS of -3.2% by cycle end. In subjects treated with CC-486 300 mg QD,14/28 days and 21/28 days, methylation was significantly reduced at Day 15 (-3.3% and -5.3%, respectively), Day 22 (-3.8% and -6.7%) and cycle end (-2.4% and -5.0%) (Laille, 2015).

Despite the reduced bioavailability of CC-486 compared to azacitidine administered subcutaneously, the oral agent, given 21/28 days, is associated with greater reductions in GDMS through the end of the treatment cycle. Twice-daily dosing may further enhance target engagement and achieve greater reductions in global methylation. In the study described above, though few subjects received BID oral dosing, the largest absolute reductions in DNA methylation were associated with BID dosing. CC-486 200 mg BID taken 21/28 days was associated with the greatest reductions in GDMS: -11.0%, -11.8%, and -9.1% at Day 15, Day 22, and Day 28, respectively (Laille, 2015).

An orally administered hypomethylating agent may offer several advantages when compared to parenterally administered agents. Oral administration eliminates the need for the patient to travel for parenteral administration. Furthermore, as no injection is needed, there is the potential to decrease adverse events at the site of injection including pain and infection.

Demethylation of several immune checkpoint genes was seen in these analyses which is in line with findings that PD-1 and PD-L1 expression was increased after treatment with HMA

(Yang, 2014). Due to these findings, it is hypothesized that CC-486 could be an effective treatment for MDS patients who have failed HMAs.

The goal in treating this population and in evaluating new potentially therapeutic options is to capture or recapture hematologic response or hematologic improvement (Appendix F), to reduce the rate of disease progression and AML transformation, and to prolong survival. Despite active interest in the post-HMA setting among researchers, there remains a critical unmet medical need.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the Investigational Product (IP). The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.4.2. Cancer and Immune Function

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan, 2000). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immune-competent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity. The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or costimulation, or by suppressing immunosuppressive factors, cells, or messages (Monti, 2005).

1.4.3. Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch, 2012; Crespo, 2013). It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn, 2004). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Wolchok, 2009; Hodi, 2010; Robert, 2011; Brahmer, 2010; Topalian, 2012). Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), PD-1, and PD-L1 have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in NSCLC (Brahmer, 2010; Brahmer, 2012; Topalian, 2012; Gordon, 2013), and prostate cancer (Harzstark, 2010). Pembrolizumab and nivolumab are both PD-1 blocking antibodies and the first in the anti-PD-1 pathway family of checkpoint inhibitors to gain approval

from the US Food and Drug Administration (FDA), pembrolizumab for melanoma and nivolumab for melanoma and squamous cell lung cancer. Both pembrolizumab and nivolumab have received European Commission regulatory approval for the treatment of metastatic melanoma. The European Commission has also approved nivolumab for the treatment of advanced previously treated squamous NSCLC.

The PD-1 receptor, in conjunction with receptor ligands PD-L1 and PD-L2, functions to regulate the immune system primarily by down regulating signals of the T-cell receptor. PD-L1 expressed on tumor cells binds to PD-1 on T-cells which leads to down-regulation of T-cell activity and allows tumor cells to evade the immune response

Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with MDS or AML. Studies in mouse models of transplantable tumors have demonstrated that manipulation of costimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs, 2009). This may be accomplished by blocking co-inhibitory molecules such as CTLA-4 or PD-1 from binding with their ligands, B7 or B7-H1 (PD-L1).

PD-L1 and PD-L2 are expressed on many human lymphomas (Li, 2012; Chen, 2013). PD-L1 has been detected on several hematologic malignancies, including Hodgkin lymphoma, primary mediastinal B-cell lymphoma, angioimmunoblastic T-cell lymphoma, multiple myeloma, acute myeloid leukemia, chronic lymphocytic leukemia, and adult T-cell leukemia/lymphoma (Liu, 2007; Dorfman, 2006; Rosenwald, 2003; Tamura, 2005; Xerri, 2008). PD-L1 expression has been detected on several myeloid cell lines, suggesting that PD-L1 expression continues to suppress immune function (Dolen, 2013). In addition, in MDS subtypes, PD-L1 expression on myeloblasts has been associated with MDS transformation to AML (Ogata, 2012). Myeloid leukemia cell lines that were treated with the hypomethylating agent decitabine were shown to have an upregulation of PD-L1 expression (Yang, 2012). Upregulation (≥ 2 fold) of PD-L1 has been observed in 25% of AML CD34+ samples, 33% of PD-L2, and 22% of PD-1 (Yang, 2014).

PD-1 signaling may be involved in MDS pathogenesis and resistance mechanisms to azacitidine; therefore, combined blockade of this pathway can be a potential therapy in MDS and AML (Yang, 2014).

PD-L1 expression is present in MDS and AML, with increased expression observed in advanced disease. In addition, there has been evidence to suggest that PD-L1 is upregulated in myeloblasts in MDS subtypes (Yang, 2014). Therefore, a rationale exists for evaluating durvalumab in combination with azacitidine in subjects with MDS and AML.

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1.4.5. Rationale for Durvalumab Fixed Dosing Regimen

The dose and schedule for durvalumab monotherapy (20 mg/kg once every 4 weeks [Q4W]) were selected based on 2 sets of data: (1) the safety analysis of doses (0.1, 0.3, 1, 3, and 10 mg/kg once every 2 weeks [Q2W]) administered in Study CD-ON-MEDI4736-1108 (a Phase 1/2 study to evaluate the safety, tolerability, and PK of IV durvalumab given as monotherapy in subjects with advanced solid tumors; and (2) PK profile simulations for durvalumab administered using 10 mg/kg Q2W and 20 mg/kg Q4W schedules.

Safety and PK characteristics of the studied dose and schedule 10 mg/kg Q2W:

After evaluation of the PK data from subjects enrolled in Study CD-ON-MEDI4736-1108, durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. Linear PK was observed at doses of 3 mg/kg and higher and is consistent with near complete target suppression, as reflected in target trough plasma concentrations of drug >100 ug/mL. This trough concentration is supported by soluble PD-L1 (sPD-L1) suppression data. Furthermore, the 10 mg/kg Q2W dose was not associated with any DLTs in the dose escalation portion and was, therefore, selected for further evaluation in the dose-expansion portion of Study CD-ON-MEDI4736-1108.

Extrapolation of dose and schedule of 10 mg/kg Q2W to 20 mg/kg Q4W through population PK modeling:

A population PK model was developed using durvalumab monotherapy data from Phase 1 of Study CD-ON-MEDI4736-1108 (N=292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors) (Fairman, 2014). This population PK model adequately described monotherapy PK data and was utilized to predict expected PK exposures following 20 mg/kg Q4W dosing regimens (since none of the monotherapy studies explored Q4W regimens). Pharmacokinetic simulations indicate that a similar overall exposure as represented by AUCs (4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens. However, median C_{max} at steady state is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median trough concentration at steady state is expected to be higher with 10 mg/kg Q2W (~1.25 fold).

Justification for fixed dosing over weight-based dosing:

Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000

subjects were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of durvalumab at 1500 mg Q4W (equivalent to 20 mg/kg Q4W) is included in the current study.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to investigate the efficacy of CC-486 as monotherapy and in combination with anti-PD-L1 monoclonal antibody, durvalumab (MEDI4736), in subjects with MDS that did not respond to prior treatment with an injectable hypomethylating agent (HMA – azacitidine for injection or decitabine), or were unable to tolerate treatment with an injectable HMA.

2.2. Secondary Objectives

The secondary objectives of the study are to:

- Assess the safety and tolerability of CC-486 alone and in combination with durvalumab, as treatment for MDS
- Describe the clinical relevance of objective hematologic and/or biologic responses associated with treatment with CC-486 alone and in combination with durvalumab
- Evaluate the impact (if any) of durvalumab on the pharmacokinetics of CC-486 and CC-486 on durvalumab in subjects with MDS

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3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of this study is the overall rate of objective response (ORR) to treatment with CC-486 monotherapy and combination therapy with CC-486 and durvalumab: the proportion of subjects achieving an objective response (hematologic improvement [HI], partial response [PR], complete remission [CR], or marrow CR) based on modified International Working Group (IWG) 2006 criteria - Appendix F.

3.2. Secondary Endpoint(s)

The secondary endpoints of this study are:

- Overall survival;
- Time to onset of responses;
- Duration of responses;
- Progression free survival (time to disease progression or death from any cause);
- Proportion of subjects with progressive disease at baseline achieving stable disease, as well as time to achieving stable disease and duration of stable disease;
- The proportion of subjects progressing to AML and time to AML progression;
- Safety and tolerability (type, frequency, severity of AEs and relationship of AEs to CC-486 and/or durvalumab; monitoring for disease progression to AML, as well as immune- and infusion-type reactions);
- Serum/plasma PK parameters for durvalumab and CC-486, including maximum observed concentration (C_{max}), AUC, time to maximum concentration (T_{max}), terminal half-life ($t_{½}$), clearance (CL/F) and volume of distribution (Vz/F).

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4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, international, multicenter, randomized, parallel group, open-label study consisting of 5 study phases: *Screening, Safety Run-in, Randomized Treatment*, *Follow-up*, and *Extension*.

The study is closed to further enrollment with the last subject enrolled in June 2018. A total of 65 subjects were enrolled in the study. At the time of this amendment, 6 subjects are ongoing in the Monotherapy SD/PD cohorts (One subject from Phase 1, and 5 from Phase 2).

The study is amended to include an Extension Phase (EP). The EP allows subjects who are currently receiving oral azacitidine and who are demonstrating clinical benefit as assessed by the Investigator, to continue receiving oral azacitidine until the subject meets the criteria for study treatment discontinuation. No survival will be followed during the EP.

A *Safety Run-in* will first explore the safety and tolerability of monotherapy, followed by combination therapy to confirm that there are no overlapping or synergistic toxicities limiting the ability of the two drugs to be delivered in combination (see Figure 1).

The randomized treatment phase of the study will be conducted in 2 stages. Following identification of dose and schedule in the safety run-in of a treatment arm, enrollment for Stage 1 of the treatment phase may begin. Eligible subjects will be randomized to one of two open treatment arms:

- Monotherapy – CC-486 alone, or
- Combination Therapy – CC-486 plus durvalumab

In the event that only one treatment arm for a cohort is open for accrual due to available safety and efficacy data, subjects will be assigned to treatment on the open arm.

Throughout the study, subjects will be categorized as having *Progressive Disease* (PD) or *Stable Disease* (SD) and these designations are made based on the subject's best response to iHMA therapy determined at the start of this study (see Section 7), and any marked changes in their disease prior to beginning treatment in this study (eg, a subject with stable disease as their best response to iHMA therapy, but with subsequent disease progression would be assigned to the PD group). Numbers of subjects with PD and SD allocated to each treatment arm will be monitored to enable the planned analyses for each sub-population. Hence there are 4 cohorts being evaluated in this study:

- Monotherapy, progressive disease
- Monotherapy, stable disease
- Combination therapy, progressive disease
- Combination therapy, stable disease

Excluded from participation in this clinical trial is the cohort of patients that initially demonstrates a positive response to treatment with an injectable HMA, but subsequently relapses. This group is thought to represent an especially difficult-to-treat sub-population in

which gaining disease control is unlikely with currently-available or experimental options. Even among patients not responding to initial HMA therapy, some will experience rapidly-progressing disease characterized by dramatic increases in myeloid precursors and blast cells in the marrow or blood.

This multi-center, international study will enroll at least 70 to 194 evaluable subjects (inclusive of subjects in the safety run-in and randomized phases).

At least 6 subjects will be included in the safety run-in: 3 receiving monotherapy, and 3 receiving combination therapy (see Figure 1). The dose and schedule of CC-486 to be evaluated in combination with a fixed dose of durvalumab will be determined as described in Section 4.1.2.

In the randomized treatment phase, eligible subjects will be randomized to receive CC-486 alone or in combination with durvalumab. The randomized treatment phase will be conducted in 2 stages, with a futility assessment planned at the completion of Stage 1 to determine whether the null hypothesis *(H_0: $p < 12.5\%$)* can be rejected with 3 or more responses in Stage 1. If 3 or more responses have been observed before the end of Stage 1, the planned futility assessment may be performed earlier than at the completion of Stage 1 to confirm the finding of responses. This earlier analysis will replace the futility analysis planned at the completion of Stage 1. This earlier futility assessment will have the same integrity as the futility assessment planned at the completion of Stage 1. An analysis will be performed at the completion of Stage 2 to estimate the overall response rate of treatment of all the subjects in the cohort (see Figure 2). Additional analyses will be conducted approximately 12 months after the last subject is enrolled, as described in Section 4.1.5 and Section 10.6.2.

During the randomized treatment phase of the study, approximately 32 subjects with PD and 32 subjects with SD will be randomized evenly to receive either CC-486 alone, or CC-486 + durvalumab. There will be 4 cohorts (16 subjects in each) in Stage 1: SD treated with monotherapy, PD treated with monotherapy, SD treated with combination therapy and PD treated with combination therapy. If there are 2 or fewer responses in any cohort during Stage 1, enrollment to that arm will be terminated. Otherwise, the cohort will continue to Stage 2 and accrue an additional 25 subjects each. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected for that cohort. During the course of the study, whenever both cohorts of the same patient classification (ie, SD or PD) are open for enrollment, established randomization procedures will be followed. During Stage 1, if a cohort is awaiting the decision to continue to Stage 2 pending on the response evaluation while the other cohort of the same patient classification is open for enrollment, available patients will be assigned to the cohort with open enrollment without randomization. If both cohorts of the same patient classification are waiting for response evaluations, enrollment of that patient classification will be temporarily halted.

Therefore, the total number of subjects for the randomized treatment phase will range from approximately 64 (at Stage 1) to 164 (Stage 1 plus Stage 2) for the 4 subject cohorts. More subjects can potentially be recruited for replacement of non-evaluable subjects, if needed (see Figure 2).

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Best supportive care measures should be used in combination with study treatment as deemed necessary. Best supportive care includes, but is not limited to, treatment with RBC transfusions (packed red blood cells [pRBC] or whole blood), single donor or pooled donor platelet transfusions, antibiotic, antiviral and/or antifungal therapy, antiemetic and/or antidiarrheal support, nutritional support as needed, and granulocyte/granulocyte macrophage colony-stimulating factors (G/GM-CSF) for subjects experiencing neutropenic fever/infection, or as secondary prophylaxis as described in Section 9.1. Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors (eg, thrombopoiesis stimulating agents).

4.1.1. Screening Phase

Screening procedures are conducted within 28 days prior to enrollment and beginning treatment in the safety run-in or treatment phase of the study to ensure that all inclusion and exclusion criteria are satisfied.

Documentation collected by the study site and laboratory values obtained from the local and/or central laboratory are used to review the subject's eligibility and baseline disease characteristics; eg, WHO/FAB classification (Appendix A / Appendix B), IPSS (Appendix C), and International Prognostic Scoring System-Revised (IPSS-R) (Appendix D) risk classification. Bone marrow biopsy and aspirate, blood, and relevant clinical documentation obtained during screening will be sent for centralized review by an independent pathologist to ensure consistency in determination of diagnosis and baseline disease characteristics. If documentation of MDS diagnosis, WHO/FAB classification and IPSS/IPSS-R risk categorization is available and within 2 months of screening, results of central review are not required prior to enrollment of the subject in the study. However, the results of central pathology review will be used in classification of subjects for analysis.

A comprehensive blood product transfusion history must be available for at least the 56 days immediately preceding and including the day of the first dose of IP. Transfusion data should include the blood product transfused, number of units, reason for transfusion, and date of transfusion. Platelet transfusion data must include the platelet value for which the transfusion was deemed necessary and RBC transfusion data must include the hemoglobin (Hgb) value for which the transfusion was administered, if available. All transfusion records for 56 days immediately preceding and including the date of enrollment should be collected whenever possible.

Screening assessments and procedures are described in Section 6.1.

4.1.2. Safety Run-in

The safety run-in will utilize a conventional 3+3 design to find a tolerable dose for the randomized treatment phase. The subjects will be treated with CC-486 first to confirm the expected safety profile of CC-486 alone at the planned dose and schedule in the target population. The maximum administered dose (MAD) of CC-486 will not exceed 300 mg BID (21/28 days). The resulting tolerable dose of CC-486 will then be used to combine with durvalumab 1500 mg for the combination therapy.

The completion of the CC-486 safety run-in has determined 100 mg BID, 21/28 day regimen (dose level -2) as the CC-486 dose to proceed into the combination therapy safety run-in.

The dose-finding procedure for CC-486 and CC-486+durvalumab will proceed as following.

Part (A) - starting dose for CC-486 as monotherapy: A group of 3 subjects will receive CC-486 at dose level 0 (200 mg BID (21/28 days) and will be closely monitored through at least 2 treatment cycles for dose-limiting toxicities, as defined in Section 4.1.2.1. If for any reason the monotherapy safety run-in starting dose needs to be reduced, the starting dose will follow the established levels in Table 1.

1. If #Subject with DLT = 0/3, the dose will be declared tolerable and used as the starting CC-486 dose.
2. If #Subject with DLT = 1/3, recruit another 3 subjects to test the same dose.
    a. If #Subject with DLT = 1/6, the dose will be declared tolerable and used as the starting CC-486 dose.
    b. If #Subject with DLT ≥ 2/6, the dose will be declared intolerable and the next lower dose level of CC-486 according to Table 1 will then be explored. Repeat the entire procedure with 3 new subjects.
3. If #Subject with DLT ≥ 2/3, the dose will be declared intolerable and the next lower dose level of CC-486 according to Table 1 will then be explored. Repeat the entire procedure with 3 new subjects.

The safety run-in for CC-486 monotherapy has been completed as of December 2016.

Part (B) - starting dose for CC-486+durvalumab as combination therapy: A group of 3 subjects will receive CC-486 dose determined in Part (A) above plus durvalumab 1500 mg (given by IV infusion [over 1 hour ± 5 minutes] on Day 1 of each 28-day treatment cycle) and will be closely monitored through at least 2 treatment cycles for dose-limiting toxicities, as defined in Section 4.1.2.1.

1. If #Subject with DLT = 0/3, the dose will be declared tolerable and used as the starting CC-486 dose plus durvalumab 1500 mg.
2. If #Subject with DLT = 1/3, recruit another 3 subjects to test the same dose.
    a. If #Subject with DLT = 1/6, the dose will be declared tolerable and used as the starting CC-486 dose plus durvalumab 1500 mg.
    b. If #Subject with DLT ≥ 2/6, the dose will be declared intolerable and the next lower dose level of CC-486 according to Table 1 plus durvalumab 1500 mg will be explored. Repeat the entire procedure with 3 new subjects.
3. If #Subject with DLT ≥ 2/3, the dose will be declared intolerable and the next lower dose level of CC-486 according to Table 1 plus durvalumab 1500 mg will be explored. Repeat the entire procedure with 3 new subjects.

Table 1: CC-486 Dose Levels for Safety Run-in

Dose Level	CC-486 Dose/Schedule	Durvalumab Dose/Schedule
0	200 mg BID; 21/28 days	1500 mg IV infusion on Day 1 of 28 day treatment cycle
-1	150 mg BID; 21/28 days	
-2	100 mg BID; 21/28 days	
-3	100 mg BID; 14/28 days	

BID = twice daily; IV = intravenous.

Subjects who discontinue participation in the safety run-in phase of the study for reasons not related to study treatment (eg, rapid disease progression or administrative reasons) before they can be assessed for DLT will be replaced for the DLT assessment.

Other than the evaluation of DLTs, procedures and assessments to be performed during the safety run-in are similar to those performed for the randomized treatment phase of the study (see Section 4.1.3).

Data from the safety run-in will be reviewed in conjunction with the study investigators, Scientific Steering Committee, and Data Monitoring Committee to ensure agreement with the recommended Phase 2 dosing regimens prior to beginning enrollment to the randomized treatment phase.

Once the recommended combination regimen is identified, enrollment into the randomized treatment phase of the study may begin.

4.1.2.1. CC-486 Monotherapy Dose-Limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the safety run-in. For CC-486, the DLT evaluation period will be defined as the time from the first dose of CC-486 until the planned first dose of IP in Cycle 3. Subjects are considered evaluable for assessment of DLT if they receive ≥ 2 protocol-assigned cycles of CC-486 and complete the safety follow-up through the end of the DLT evaluation period, or experience a DLT during the DLT evaluation period. Non-evaluable subjects will be replaced.

For CC-486, a DLT will be defined as:

- Grade 5 hematologic events;
- Grade 4 neutropenia lasting > 10 days or accompanied by fever (defined as ≥ 38.5°C requiring hospitalization);
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding and,
- Any Grade ≥ 3 non-hematologic toxicity or hematologic toxicity other than anemia or cytopenia with the following exceptions:
  - Grade 3 emesis that responds to optimal antiemetic therapy within 72 hours;
  - Grade 3 diarrhea that responds to optimal medical management within 72 hours;

- Grade 3 fatigue in a subject who had Grade 2 fatigue at study entry and that recovers to baseline grade or less within 72 hours;
- Grade 3 or 4 laboratory abnormalities that are not accompanied by clinical signs or symptoms and are not believed by the Investigator to be medically significant.

Grade 3 or 4 events clearly and directly related to the primary disease or to another etiology documented by the investigator are not considered DLTs.

Table 4 provides guidance for the management of CC-486-related toxicity, including provisions for appropriate delay or discontinuation of treatment.

For acute events of neutropenia, thrombocytopenia, and leucopenia, associated with treatment with CC-486, the following formula should be used to calculate the minimum neutrophil, platelet, or white blood cell count that would signify "recovery" of marrow function and enable initiation of the subsequent treatment cycle.

$$\textit{Recovery} = \begin{array}{l}\text{ANC,}\\ \text{HgB, or}\\ \text{Platelet}\\ \text{count}\end{array} \geq \text{Nadir count} + \frac{(\text{Baseline count} - \text{Nadir count})}{2}$$

For example, a subject with a pre-treatment absolute neutrophil count (ANC) of 1.0 x 10^9/L experiences a nadir ANC of 0.4 x 10^9/L (Grade 4) following one cycle of treatment. The subject's ANC must recover to at least 0.4 + (1.0-0.4)/2, or 0.7 x 10^9/L before beginning the subsequent treatment cycle. If the event is judged by the investigator to be related to study treatment and recovery is not achieved within 14 days of completing Cycle 1, it will be considered a dose-limiting toxicity.

4.1.2.2. Durvalumab / CC-486 Combination Therapy Dose-Limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the safety run-in. Please refer to Section 4.1.2.1 for CC-486 related dose-limiting toxicity criteria.

For durvalumab, the DLT evaluation period will be defined as the time from the first dose of durvalumab until the planned administration of the third dose of durvalumab. Subjects are considered evaluable for assessment of DLT if they receive 2 protocol-assigned doses of durvalumab and complete the safety follow-up through the end of the DLT evaluation period, or experience a DLT during the DLT evaluation period. Non-evaluable subjects will be replaced.

The severity grading of adverse events will be determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

For durvalumab, a DLT will be defined as any Grade 3 or higher durvalumab-related toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the

primary disease or to another etiology is excluded from this definition. The following will be considered DLTs:

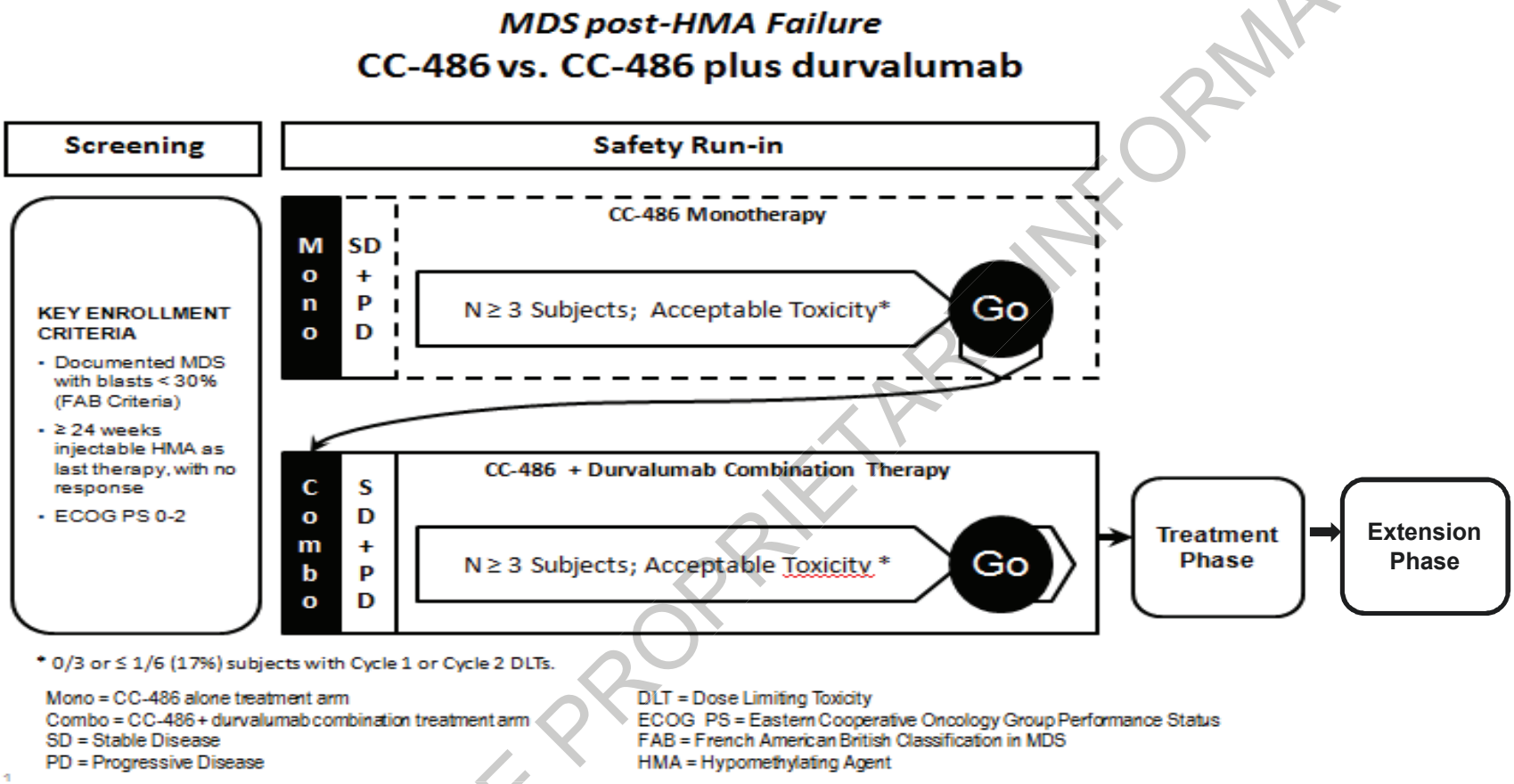
- Liver transaminase elevation ≥ 5 x but ≤ 8 x the upper limit of normal (ULN) that does not downgrade to Grade 2 within 5 days after onset with optimal medical management, which may include systemic corticosteroids. Transaminase elevation > 8 x ULN or total bilirubin > 5 x ULN will be considered a DLT regardless of duration or reversibility.
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 7 days of the initiation of maximal supportive care.

The definition excludes the following conditions:

- Grade 3 fatigue for ≤ 7 days
- Grade 3 or 4 nausea or vomiting that resolves to ≤ Grade 2 with optimal symptomatic treatment
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject becomes asymptomatic
- Grade 3 inflammatory reaction attributed to an antitumor response (eg, inflammatory reaction at sites of lymphomatous disease, etc.) that resolves to ≤ Grade 1 within 30 days
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Any Grade 3 electrolyte alteration that is reversible to ≤ Grade 1 within 72 hours after onset
- Grade 3 amylase and/or lipase elevation that is not associated with clinical symptoms or radiographic changes suggestive of pancreatitis
- Any ≥ Grade 3 lymphopenia (unless clinically significant)
- Grade 3 or 4 neutropenia in the absence of fever or infection that resolves to ≤ Grade 2 within 7 days after onset
- Grade 3 or 4 thrombocytopenia without evidence of bleeding that resolves to Grade 2 within 7 days after onset and does not require a transfusion
- Grade 3 anemia that resolves to ≤ Grade 2 within 7 days without transfusion support
- Grade 3 fever lasting ≤ 24 hours with or without medical therapy and is not considered an SAE
- Grade 3 rigors or chills lasting < 6 hours that respond to optimum medical therapy
- Grade 3 tumor lysis syndrome that resolves to ≤ Grade 2 within 72 hours after initiation of maximal medical intervention

Immune-mediated adverse events are defined as AEs of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. An AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

Figure 1: Safety Run-in Phase Study Design



4.1.3. Randomized Treatment Phase

Figure 2 depicts the study design of the randomized treatment phase.

The randomized treatment phase of the study will be conducted in 2 stages. Following identification of dose and schedule in the safety run-in of a treatment arm, enrollment for Stage 1 of the treatment phase may begin. Eligible subjects will be randomized to one of two open treatment arms:

- Monotherapy – CC-486 alone, or
- Combination Therapy – CC-486 plus durvalumab

In the event that only one treatment arm for a cohort is open for accrual due to available safety and efficacy data, subjects will be assigned to treatment on the open arm.

Subjects with stable disease at the time of enrollment will be included in the *stable disease* (SD) cohort for that treatment arm, and those with progressive disease at the time of enrollment will be included in the *progressive disease* (PD) cohort (see Section 7.2). Subjects with MDS that responded to injectable HMA treatment are not eligible for this study, even if their disease subsequently relapsed.

Numbers of subjects with PD and SD allocated to each treatment arm will be monitored to enable the planned analyses for each sub-population. Hence there are 4 cohorts being evaluated in this study:

- Monotherapy, progressive disease
- Monotherapy, stable disease
- Combination therapy, progressive disease
- Combination therapy, stable disease

Excluded from participation in this clinical trial is the cohort of patients that initially demonstrates a positive response to treatment with an injectable HMA, but subsequently relapses. This group is thought to represent an especially difficult-to-treat sub-population in which gaining disease control is unlikely with currently-available or experimental options. Even among patients not responding to initial HMA therapy, some will experience rapidly-progressing disease characterized by dramatic increases in myeloid precursors and blast cells in the marrow or blood.

All baseline assessments and procedures should be performed prior to administration of the first dose of CC-486 or infusion of durvalumab.

The subject should begin treatment on the day of randomization via Interactive Response Technology System (IRTS) whenever possible, but the dose may be delayed for up to 5 days if necessary for logistical reasons. Any delay greater than 5 days must be discussed with, and approved by, the sponsor's medical monitor and may result in the need to repeat screening.

Approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected centers will participate in PK sampling procedures as described in Sections 4.1.4 and 6.10. Subjects in whom Cycle 1 and 2 PK sampling cannot be completed will be replaced for PK collection purposes.

A subject's CC-486 dose and schedule may be adjusted as described in Section 8.2.4 for the management of unacceptable toxicity. All efforts should be made to maintain BID dosing. A QD 'rescue' regimen is available if the investigator believes a subject's ability to tolerate treatment is limited by twice-daily dosing (see Table 3). Subjects who cannot tolerate a reduced dose and schedule of 100 mg BID (or 200 mg QD), 14/28 days, will discontinue the treatment phase of the study and enter the follow-up phase.

Interruption or delay of treatment with CC-486 for up to 42 days is permitted as outlined in Section 8.2.4.1 to enable recovery from IP-related toxicity. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the medical monitor must be consulted. When the start of a new treatment cycle with CC-486 is delayed for any reason, the infusion of durvalumab will also be delayed (in subjects randomized to the combination treatment arm), such that durvalumab continues to be administered on Day 1 of each treatment cycle. Study treatment should be discontinued if there is a delay of more than 56 days (8 weeks) in the start of the next cycle, unless, in the opinion of the investigator and the medical monitor, the subject is experiencing clinical benefit.

For toxicity that is thought to be related to treatment with durvalumab, including immune-mediated AEs (imAEs) or infusion-type reactions, as well as for non-immune mediated reactions, the infusion of durvalumab may be slowed or interrupted, or a dose may be withheld, as described in Section 8.2.4.2. Dose reduction of durvalumab is not permitted.

In the absence of unacceptable toxicity, subjects who show signs of worsening disease (clinical or hematological), who remain in stable disease, or do not experience modified IWG 2006 hematologic improvement (HI) or better (PR, CR or marrow CR – modified IWG 2006, Appendix F) after 2 well-tolerated cycles, may have their **dose increased** at the discretion of the investigator and in discussion with the medical monitor as described in Section 6.5 and Table 3. Again, dose and schedule may be adjusted as described in Section 8.2.4 in order to manage toxicity.

Visits during the randomized treatment phase are scheduled weekly for the first 2 treatment cycles, every 2 weeks for the next 10 cycles and monthly once a subject has completed 12 cycles.

During treatment, subjects will be assessed continuously for safety and efficacy. Assessments and procedures include:

- AEs including AESI
- physical examination
- vital signs
- ECG (screening and treatment discontinuation visit only)
- body weight measurement
- Eastern Cooperative Oncology Group (ECOG) performance status
- cytogenetics
- blood and bone marrow sampling for biomarker analysis
- general disease status assessment
- modified IWG response assessment
- IP dispensation, administration and accountability
- infusion monitoring for those receiving durvalumab

- concomitant medications, therapies and procedures
- transfusion assessment
- hematology assessments via central lab
- peripheral blood smear
- serum chemistry (to include amylase and lipase), thyroid function parameters via central lab
- urinalysis
- pregnancy testing (females of child bearing potential [FCBP] only)
- bone marrow aspirate (or biopsy if an adequate aspirate cannot be obtained)
- subsequent MDS therapies (treatment discontinuation visit only)
- immunogenicity assessment CCI [redacted]
- PK sample collection in subjects receiving combination therapy at selected study centers

Because a hematologic response to treatment with durvalumab and/or CC-486 may be delayed, it is recommended that subjects receive at least 6 cycles of treatment with the IP; however, subjects may be discontinued from treatment at the investigator's discretion prior to reaching the recommended minimum number of cycles for any of the reasons detailed in Section 12.

Subjects' general disease status will be assessed based on available clinical and laboratory data at the end of Cycle 6, prior to starting Cycle 7.

Subjects who satisfy any one of the following criteria may continue on to Cycle 7 and beyond. The disease status of these subjects will be assessed at the beginning of every new cycle based on available clinical and laboratory assessments:

- Objective response to treatment: CR, marrow CR (mCR), PR, or HI (Appendix F), or
- RBC-transfusion-independence, or
- ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
- any other clinical benefit, including no evidence of progressive disease (see Table 8 for definitions of progressive disease).

Thereafter, a subject may be discontinued from treatment with IP for any of the reasons detailed in Section 12.

Subjects who fail to meet these criteria at the end of Cycle 6 will discontinue IP at that time and enter the follow-up phase of the study.

In the event that a subject assigned to the combination treatment arm discontinues treatment with durvalumab or CC-486 because of drug-related toxicity, treatment with CC-486 or durvalumab monotherapy may continue until any discontinuation criterion is met (see Section 12).

Prior to discontinuing treatment for a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

All subjects who have received at least one dose of IP will undergo treatment discontinuation procedures (Section 6.13) when treatment with IP is discontinued. If a subject is discontinued during a regularly-scheduled visit, that visit will be considered the treatment discontinuation visit and all treatment discontinuation procedures should be completed. If a procedure had been performed within 7 days of the treatment discontinuation visit, it does not need to be repeated.

For all enrolled/randomized subjects, the reason for discontinuing treatment will be recorded in the case report form (CRF) and in the source document, regardless of whether or not a dose of IP was ever administered.

During the randomized treatment phase of the study, approximately 32 subjects with PD and 32 subjects with SD will be randomized evenly to receive either CC-486 alone, or CC-486 + durvalumab. There will be 4 cohorts (16 subjects in each) in Stage 1: SD treated with monotherapy, PD treated with monotherapy, SD treated with combination therapy and PD treated with combination therapy. If there are 2 or fewer responses in any cohort during Stage 1, enrollment to that arm will be terminated. Otherwise, the cohort will continue to Stage 2 and accrue an additional 25 subjects each. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected for that cohort.

Therefore, the total number of subjects for the randomized treatment phase will range from approximately 64 (at Stage 1) to 164 (Stage 1 plus Stage 2) for the 4 cohorts. More subjects can potentially be recruited for replacement of non-evaluable subjects, if needed (see Figure 2).

A subject is considered evaluable for response once they have received one cycle of treatment with a maximum of 6 cycles of treatment, or have discontinued from the treatment phase for any reason. A subject who discontinues from the treatment phase for any reason not related to IP toxicity (eg, disease progression or administrative reasons) before the first post-baseline efficacy assessment (following treatment Cycle 2) will be replaced and an additional subject will be included in that cohort (PD or SD cohort). This will ensure a valid statistical assessment in both the intent-to-treat (ITT) population, and, if different, the modified ITT (mITT) population (Section 10.2), excluding those who discontinue study treatment early because of the rapid progression of their disease, or leave the study for non-study-related reasons prior to this first post-baseline efficacy assessment.

The sponsor, in consultation with the Scientific Steering Committee and Independent Data Monitoring Committee, will continue to evaluate each subject's response to treatment based on modified IWG 2006 criteria (Appendix F) until the required number of responses is observed for a given cohort to proceed to Stage 2, or when the last active subject in Stage 1 of any cohort (monotherapy or combination therapy; PD or SD) reaches the disease status assessment following treatment Cycle 6. At that point a final determination can be made regarding the progression of that cohort to Stage 2.

In addition to evaluating responses to treatment based on objective criteria, the sponsor, in consultation with the Scientific Steering Committee and Independent Data Monitoring Committee, will also evaluate the quality of each objective response. *Quality of response* will be

assessed based on the magnitude of hematologic and biologic responses observed in individual subjects, with special consideration for response duration. The sponsor may decide to discontinue accrual to one or both cohorts despite observing the required number of objective responses if the responses are not thought to be clinically relevant. For example, if a sufficient quantity of responses is observed, but all responses are transient hematologic improvements that are not thought to convey a meaningful benefit for the subject, the sponsor may choose to not continue enrollment to that cohort in Stage 2. Specific details for what constitutes a *quality response* will be provided in the final Statistical Analysis Plan (SAP).

4.1.4. Pharmacokinetics Sub-study

Blood samples for pharmacokinetic analysis will be collected from approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected sites. This will enable assessment of drug-drug interactions. Subjects participating in PK procedures will agree to have blood samples collected as described in Section 6.10.

All subjects receiving durvalumab will have blood samples collected for assessment of immunogenicity: development of anti-durvalumab antibodies. CCI [redacted].

4.1.5. Follow-up Phase

4.1.5.1. Follow-up in Subjects Receiving CC-486 Monotherapy

All subjects who receive at least one dose of CC-486 in the safety run-in or randomized treatment phase and discontinue treatment for any reason will be followed for at least 28 days after their last dose of CC-486 for the assessment of safety-related parameters (see Section 6.14). After the 28-day period, only SAEs made known to the investigator that are suspected of being related to treatment with CC-486 need to be reported.

A 28-day follow-up visit will be conducted 28 (±3) days following the last dose of CC-486 or during the final treatment phase study visit (whichever date is later) for assessment of the following safety-related parameters (see Section 6.14).

- Survival,
- AEs including AESI
- Concomitant medications, therapies, and procedures,
- RBC and platelet transfusions,
- New MDS therapies, or
- Disease progression to AML

Subjects in follow-up will then be contacted every 3 months from the date of the 28-day follow-up visit until death, loss-to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to:

- Survival

- Subsequent MDS-related therapies
- Disease progression to AML.

This will continue until the last active subject completes approximately 12 months of treatment and/or follow-up unless additional follow-up is needed to evaluate time-to-event endpoints (eg, progression-free survival [PFS] and survival). Follow-up contacts will routinely be conducted by telephone unless special circumstances exist (eg, the subject will visit the center for a non-study-related reason).

Females of childbearing potential should avoid becoming pregnant for 90 days after the last dose of IP and male subjects should avoid fathering a child for 90 days after the last dose of IP.

4.1.5.2. Follow-up in Subjects Receiving Durvalumab / CC-486 Combination Therapy

All subjects who receive at least one dose of durvalumab in the safety run-in or randomized treatment phase and discontinue treatment for any reason will be followed for at least 90 days after their last infusion of durvalumab for the assessment of safety-related parameters (see Section 6.14). After the 28-day period for CC-486 and the 90-day period for durvalumab, only SAEs made known to the investigator that are suspected of being related to study treatment need to be reported.

Subjects are to return to the study site 28 (±3) days after the End of Trial (EOT) visit and 90 (±3) days after the last dose of durvalumab for assessment of the following safety-related parameters:

- Survival,
- AEs including AESI (monitored until 28 days after last dose of CC-486 and 90 days after last dose of durvalumab),
- Concomitant medications, therapies, and procedures (monitored until 90 days after last dose of durvalumab),
- RBC and platelet transfusions,
- New MDS therapies, or
- Disease progression to AML

Subjects in follow-up will then be contacted every 3 months from the date of the 90-day follow-up visit until death, loss-to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to:

- Survival
- Subsequent MDS-related therapies
- Disease progression to AML.

This will continue until the last active subject completes approximately 12 months of treatment and/or follow-up unless additional follow-up is needed to evaluate time-to-event endpoints (eg, PFS and survival). Follow-up contacts will routinely be conducted by telephone unless special circumstances exist (eg, the subject will visit the center for a non-study-related reason).

Females of childbearing potential should avoid becoming pregnant for 90 days after the last dose of IP and male subjects should avoid fathering a child for 90 days after the last dose of IP.

4.1.6. Extension Phase

The Extension Phase (EP) allows subjects who are receiving oral azacitidine and demonstrating clinical benefit as assessed by the Investigator, to continue to receive oral azacitidine until they meet the criteria for study treatment discontinuation.

Subjects will remain at the same dose levels from the main study during the Extension Phase and may decrease dose levels following dose modifications (Section 8.2.4); however, dose levels will not increase. Any potential dose escalation will be considered a treatment failure and the subject should be discontinued.

Survival will not be followed in the Extension Phase.

Details for the EP are provided in Appendix J.

4.1.7. Study Closure

The study will conclude once all subjects have completed or discontinued from the Extension Phase.

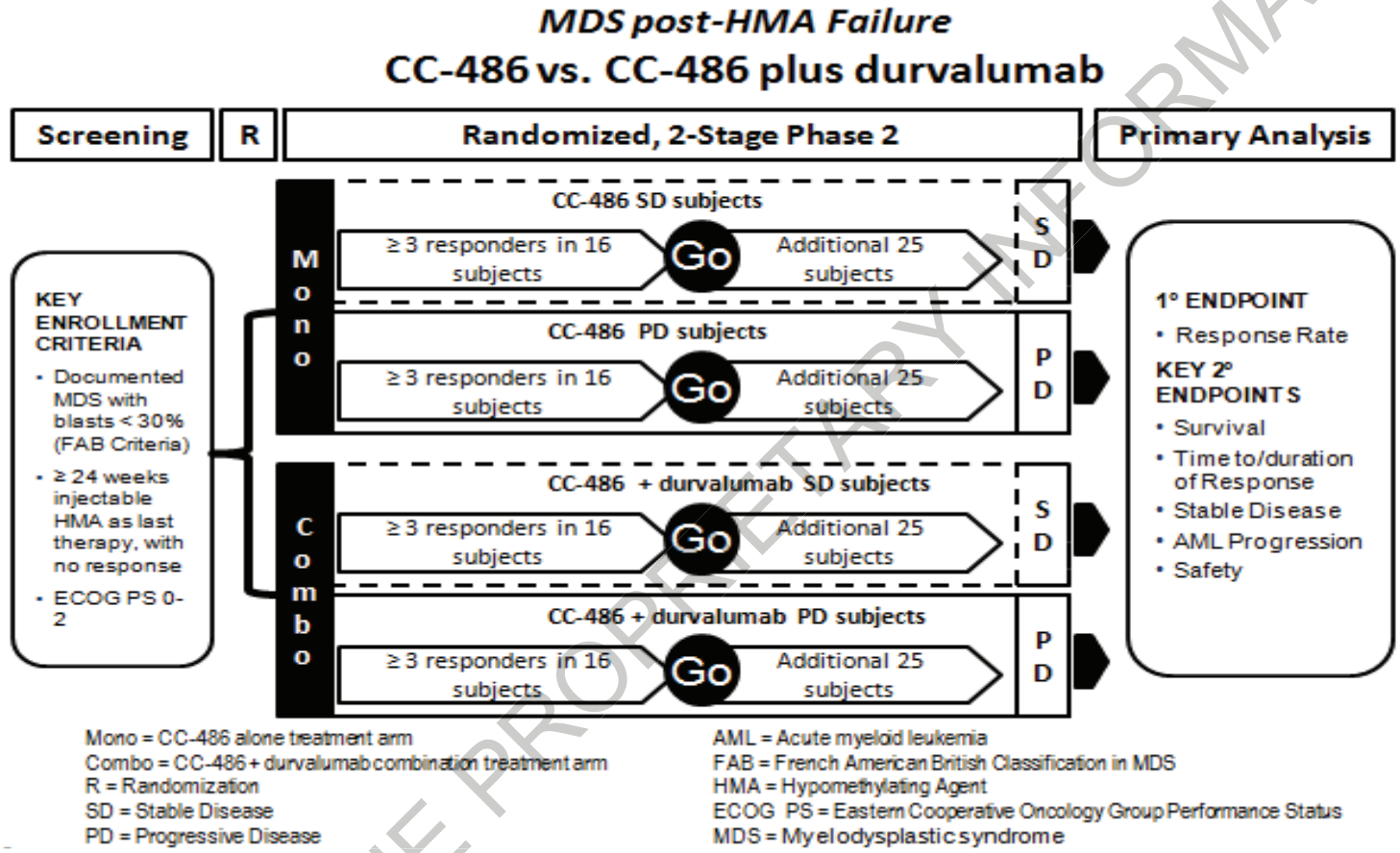
The study is expected to close when the last subject completes approximately 12 months of treatment and/or follow-up, unless additional follow-up is needed to analyze time-to-event endpoints. At the investigator's discretion, upon completion of the study, subjects who continue to benefit from treatment with CC-486 and/or durvalumab, without unacceptable toxicities and who have not met criteria for treatment withdrawal may continue to receive CC-486 and durvalumab provided by the sponsor through this protocol or through an open-label 'rollover' study.

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

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

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

Figure 2: Randomized Treatment Phase Study Design



4.2. Study Design Rationale

This is a Phase 2, international, multicenter, randomized, parallel group, open-label study designed to evaluate the efficacy and safety of treatment with CC-486 (an orally-available cytidine analog) alone and in combination with durvalumab (a monoclonal antibody targeting the Programmed Cell Death Ligand 1 [PD-L1]) in subjects with myelodysplastic syndromes when an objective response is not achieved through treatment with an injectable hypomethylating agent (iHMA). The randomized study design reduces bias in subject selection by treatment group, and enables a valid comparison of efficacy and safety between treatment groups. This will allow for selection of the appropriate treatment group for further evaluation in the post-iHMA setting.

The study population represents the group of patients with MDS that have exhausted available HMA treatment options. No additional medical intervention is currently approved in this setting and prognosis for members of this population is dismal.

The study will evaluate the two treatment regimens in two subsets of subjects who fail to respond to iHMA treatment: those with *stable disease* (with no hematologic response or improvement) associated with the iHMA, and those with *disease progression* during or following iHMA treatment. The study excludes subjects who respond to injectable therapy but subsequently relapse, because this group is thought to represent an especially hard-to-treat segment of the population where additional disease control is generally unlikely with this, or other, experimental agents. The SD and PD sub-populations will be analyzed separately for the monotherapy and combination therapy treatment arms.

A safety run-in phase of the study will explore the safety and tolerability of CC-486 alone and in combination with durvalumab to confirm that there are no overlapping or synergistic toxicities limiting the ability of the two drugs to be delivered in combination, and to determine the initial dose and schedule to be applied for the randomized portion of the study. Once a recommended dose and schedule for the combination has been identified as described in Section 4.1.2, enrollment into the randomized treatment phase may begin.

All cohorts will be evaluated using a Simon's 2-stage design (Section 10.3). This approach will enable safety and efficacy to be formally evaluated following enrollment of Stage 1 for each cohort. In this way, the sponsor can determine if exposure of additional subjects to CC-486 alone or in combination with durvalumab is warranted based on the accumulating data from subjects enrolled in Stage 1. Approximately 64 evaluable subjects will be enrolled in the first stage of the randomized treatment phase. If sufficient objective responses are observed in one or more cohorts (SD monotherapy, PD monotherapy, SD combination therapy, PD combination therapy), the applicable cohort(s) will be expanded in the second stage of study to include up to approximately 25 additional subjects per cohort (see Section 4.1, Section 10.3, and Figure 2).

In addition to evaluating responses to treatment based on objective criteria, the sponsor, together with the study's Scientific Steering Committee and Independent Data Monitoring Committee will also evaluate the quality of each objective response. *Quality of response* will be assessed based on the magnitude of hematologic and biologic responses observed in individual subjects, with special consideration for response duration. The sponsor may decide to discontinue accrual to one or more cohorts despite observing the required number of objective responses if the responses are not thought to be clinically relevant. For example, if a sufficient quantity of responses is observed, but all responses are transient hematologic improvements that are not

thought to convey a meaningful benefit for the subject, the sponsor may choose not to continue enrollment to that cohort in Stage 2.

The first dose and schedule for CC-486 to be tested in the safety run-in phase is 200 mg BID for the first 21 days of each 28-day treatment cycle. This dose and schedule has demonstrated reasonable tolerability in a prior study (Garcia-Manero, 2009; Garcia-Manero, 2010) and BID dosing is hypothesized to contribute to anti-tumor activity by affecting more malignant cells in S-phase throughout the treatment cycle compared to a once daily or injectable regimen.

Durvalumab will be administered on Day 1 of each 28-day treatment cycle as a single 1500 mg IV infusion, as described in Section 8.2.2.2.

Subjects should continue to receive IP for at least 6 cycles of treatment before considering treatment discontinuation for lack of clinical activity because, based on prior studies with parenteral azacitidine therapy, response to treatment may be delayed to allow for adequate cell line recovery without dose reduction (Silverman, 2006). While on treatment, subjects will continue to receive best supportive care, thus the requested 6-month minimum treatment period does not represent an undue risk to subjects. In addition, because overall survival is one of the endpoints, the effect of extended therapy is being evaluated; suspension of therapy at an early time point may blunt any possible clinical benefit.

Analysis of the primary endpoint will be conducted only after all active subjects have completed the modified IWG response assessment following a maximum of 6 cycles of therapy.

Best supportive care provided to all study subjects is to include RBC (pRBC and whole blood) and platelet transfusions (single donor or pooled donor), antibiotic, antiviral and antifungal therapy, and nutritional support as needed. Granulocyte colony-stimulating factors are allowed only for subjects experiencing neutropenic fever/infection as well as for secondary prophylaxis under certain conditions (see Section 9.1).

Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors as these therapies are not approved for the treatment of MDS and do not increase platelet counts in patients with concomitant thrombocytopenia associated with MDS. Furthermore, ESAs are less effective for RBC transfusion-dependent anemia than for RBC transfusion-independent anemia (Hellstrom-Lindberg, 2003). Thus the best supportive care for this study should minimize the risk of not providing subjects with appropriate care, while providing the potential benefit of achieving additional disease control that was previously not achievable. Further consideration for excluding the use of ESAs from best supportive care is the theoretical possibility that the combination of ESA with azacitidine may have an additive effect on response and this could confound the evaluation of efficacy associated with CC-486 itself. Thus excluding the use of ESAs from best supportive care would mitigate any possible bias in data interpretation, and allow accurate assessment of study endpoints.

4.3. Study Duration

The enrollment period for this study is expected to last approximately 39 months. The treatment and follow-up phases of study are expected to conclude approximately 12 months after the last subject is enrolled. The Extension Phase is expected to last approximately 24 months. Therefore, the total duration of the study is expected to be approximately 75 months.

At the investigator's discretion, upon completion of the study, subjects who continue to benefit from treatment without unacceptable toxicities, and who have not met criteria for treatment withdrawal may continue to receive IP provided by the sponsor through this protocol or through an open-label 'rollover' study.

4.4. End of Trial

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

The study will conclude once all subjects have completed or discontinued from the EP.

5. TABLE OF EVENTS

Table 2 provides a detailed description of all study events or procedures by time point for each 28-day treatment cycle.

Table 2: Table of Events

Procedure/Assessment	Screening	Safety Run-in or Treatment Phase [a]						Follow-up Phase [b]	
	≤ 28 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 12		Cycles 13+	Treatment D/C [d]	Safety Follow-up Visit(s)[x]	Additional Follow-up Contacts
		Day 1[c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
Study Entry Assessments									
Informed Consent	×	--	--	--	--	--	--	--	--
Inclusion and Exclusion Criteria	×	--	--	--	--	--	--	--	--
MDS Diagnosis (WHO and FAB Classifications) and IPSS/IPSS-R Scores	×[e]	--	--	--	--	--	--	--	--
RBC and Platelet Transfusion History	×[f]	--	--	--	--	--	--	--	--
Demographics and Medical History	×	--	--	--	--	--	--	--	--
Prior Treatment for MDS	×[g]	--	--	--	--	--	--	--	--
Prior General Medications	×[h]	--	--	--	--	--	--	--	--
Examinations									
Physical Examination	×	×	--	×	--	×	×	×	--
Vital Signs [i]	×	×	--	×	--	×	×	×	--
Body Weight	×	×	--	×	--	×	×	×	--
Height	×	--	--	--	--	--	--	--	--
ECOG Performance Status	×	×	--	×	--	×	×	×	--
Electrocardiogram – Local	×[j]	--	--	--	--	--	×	--	--
Laboratory Assessments									
Urinalysis	×[k]	--	--	×[k]	--	×[k]	×	×	--

Table 2: Table of Events (Continued)

Procedure/Assessment	Screening	Safety Run-in or Treatment Phase [a]						Follow-up Phase [b]	
	≤ 28 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 12		Cycles 13+	Treatment D/C [d]	Safety Follow-up Visit(s) [x]	Additional Follow-up Contacts
		Day 1 [c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
Serum EPO, Ferritin and Transferrin Saturation (Fe/TIBC)	× [l]	--	--	--	--	--	--	--	--
Hematology [m]	×	×	×	×	×	×	×	×	--
Coagulation Parameters	×	--	--	--	--	--	--	--	--
Serum Chemistry and Thyroid Function [n]	×	×	×	×	--	×	×	×	--
Pregnancy Testing (FCBP only) [o]	×	×	--	×	--	×	×	×	--
Safety Assessments									
Assessing Adverse Events including AESIs	After signing ICD, until 28 days after the last dose of CC-486 (90 days after the last dose of durvalumab) or the last study visit, whichever date is later								--
Monitoring for Progression to AML	After signing ICD and until death, loss to follow-up, withdrawal of consent for further data collection, or study closure								
Concomitant Medications, Therapies, and Procedures	--	From the first dose of IP until 28 days after the last dose of CC-486 (90 days after the last dose of durvalumab) or the last study visit, whichever date is later							--
Disease Assessments									
Bone Marrow Aspirate and/or Biopsy [p]	×	--	--	× [p]	--	× [p]	×	--	--
Peripheral Blood Smear [p]	×	--	--	× [p]	--	× [p]	×	--	--
Cytogenetic Testing [p]	×	--	--	× [p]	--	× [p]	×	--	--
CCI									

Table 2: Table of Events (Continued)

Procedure/Assessment	Screening	Safety Run-in or Treatment Phase [a]						Follow-up Phase [b]	
	≤ 28 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 12		Cycles 13+	Treatment D/C [d]	Safety Follow-up Visit(s) [x]	Additional Follow-up Contacts
		Day 1 [c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
Durvalumab ADA (Immunogenicity) CC [redacted]	--	C1D1 C2D1	--	C4D1 C6D1 C10D1	--	C14D1	--	--	--
Pharmacokinetics (select subjects in combination treatment arm only) [q]	C1D-1	C1D1, C2D1 Note: also collect PK on C1D3 and C2D3	C1D8, C1D15, C1D22, C2D8, C2D15, C2D22	--	--	--	--	--	--
IP Administration and Accountability									
CC-486 Dispensation [r]	--	×	--	×	--	×[y]	--	--	--
CC-486 Administration [s]	--	Day 1 to Day 21 of each 28-day treatment cycle					--	--	--
Durvalumab Administration (combination treatment arm only)	--	×	--	×	--	×	--	--	--
Durvalumab Infusion Observation (combination treatment arm only)	--	×	--	×	--	×	--	--	--
IP Accountability	--	×[t]	--	×	--	×[y]	×[y]	--	--
Response Assessments									
Transfusion Assessment [u]	--	From the first dose of IP (C1D1) until 90 days after the last dose of IP or the last study visit, whichever date is later							--
IWG Response Assessment [v]	--	×	--	×	--	×	×	--	--
General Disease Status Assessment [w]	--	--	--	×	--	×	×	--	--

Table 2: Table of Events (Continued)

Procedure/Assessment	Screening	Safety Run-in or Treatment Phase [a]						Follow-up Phase [b]	
	≤ 28 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 12		Cycles 13+	Treatment D/C [d]	Safety Follow-up Visit(s)[x]	Additional Follow-up Contacts
		Day 1[c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
Subsequent MDS Therapies	--	--	--	--	--	--	×	×	×
Survival	--	--	--	--	--	--	--	--	×

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; AESIs = adverse events of special interest; AML = acute myeloid leukemia; CRF = case report form; CxDx = Day x of Cycle x; D/C = discontinuation; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; FAB = French-American-British myelodysplastic syndrome classification system; FCBP = female of childbearing potential; Fe/TIBC = serum iron/serum total iron-binding capacity; ICD = informed consent document; IP = investigational product; IPSS(-R) = International Prognostic Scoring System (-Revised); IRTS = Interactive Response Technology System; IWG = International Working Group; MDS = myelodysplastic syndromes; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cell; WHO = World Health Organization.

[a] One cycle (28 days or 4 weeks) is considered one month. The acceptable study visit window in the treatment phase is ±3 days for Cycles 1 and 2, and; ±7 days for Cycle 3 and beyond, unless otherwise noted for a particular assessment. Study visits should also take into account the subject's IP supply. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each cycle. Day 1 of Cycles 2 and beyond may be delayed from Day 28 of the prior cycle in order for subjects to recover from toxicity and meet criteria for re-treatment (see Section 8.2.5).

[b] The study visit window for the 28-day Follow-up Visit is ±3 days. If the visit is conducted prior to post-treatment Day 28, the subject should be contacted on or after post-treatment Day 28 to obtain any new or updated information related to survival, AEs, concomitant medications, blood product transfusions, additional MDS therapies, and/or disease progression to AML. Additional follow-up contacts may be conducted by telephone and are performed every 3 months (12 weeks ± 14 days) from the date of the 28-day follow-up visit (90 days for durvalumab) until the last active subject reaches approximately 12 months of treatment, or until death, loss to follow-up, withdrawal of consent to further contact or study closure (Section 6.14).

[c] The first dose of IP in Cycle 1 should be administered on the day of entering the subject in the treatment phase via IRTS, but may be administered up to 5 days later if necessary for logistical reasons (see Section 6.3). Physical examination, ECOG performance status, hematology and/or serum chemistry do not need to be repeated if the screening examination was performed within 7 days of the first dose and all necessary parameters were assessed. Pregnancy test does not need to be repeated if the screening assessment was performed within 72 hours of the first dose of IP.

[d] All subjects who received at least one dose of IP should complete the Treatment Discontinuation Visit when the decision to discontinue IP is made. If this is during a regularly-scheduled study visit, that visit will be considered the Treatment Discontinuation Visit, and all indicated procedures performed. The reason for discontinuation will be recorded in the CRF and in the source document for all enrolled subjects, even if they never received IP. Reasons for discontinuation are provided in Section 12.

[e] Documentation supporting MDS diagnosis (WHO and FAB classifications - Appendix A and Appendix B), and IPSS/IPSS-R risk classification (Appendix C and Appendix D) will be collected during screening. If documentation of MDS diagnosis, WHO/FAB classification and IPSS/IPSS-R risk categorization is available and within 2 months of screening, results of central review are not required prior to enrollment of the subject in the study. However, the results of central pathology review will be used in classification of subjects for analysis. These assessments will be independently-confirmed through central review of screening bone marrow biopsy, aspirate, and peripheral blood samples, along with applicable central laboratory results and relevant clinical documentation. Thus, bone marrow aspirate and biopsy samples, together with peripheral blood samples and clinical documentation, must be collected during screening, as detailed in Section 6.1.15. Blood samples at screening should be collected on the same day as the bone marrow procedure. Instructions for submission of bone marrow slides and sample collection, processing, storage, and shipment procedures are provided in the Central Laboratory Manual.

[f] A comprehensive red blood cell and platelet transfusion history must be available for the 56 days immediately preceding the subject's first dose of IP and will be recorded on the appropriate CRF.

[g] All prior treatments for MDS, regardless of discontinuation date of treatment, must be recorded as detailed in Section 6.1.4.

h. All non-MDS medications taken in the 4 weeks (28 days) prior to initiation of IP are to be collected on the appropriate CRF.

i. Vital signs include measurements of blood pressure, pulse, body temperature and respiratory rate as detailed in Section 6.1.7.

j. 12-lead electrocardiogram will be performed locally at screening and upon treatment discontinuation, and if clinically indicated. The investigator will review and assess the results as detailed in Section 6.1.9.

k. Urinalysis is conducted at the central laboratory. Urine samples should be collected during screening, prior to administration of IP on Day 1 of every 3rd treatment cycle (ie, Cycle 3, 6, 9, etc.), and as indicated in the table above (see also Section 6.1.10).

l. Serum EPO, ferritin, and transferrin saturation (Fe/TIBC) assessments are to be performed by the central laboratory. It is not necessary to obtain these values if they were assessed within 2 months prior to screening (date of informed consent signature) and values are documented in the subject's medical record.

m. Hematology includes a complete blood count with WBC differential and platelets as detailed in Section 6.1.12. Any or all laboratory assessments may be repeated more frequently if clinically indicated. All samples will be analyzed by the central laboratory. The samples are to be collected at screening, prior to IP administration as detailed in Section 6, and at the treatment discontinuation and 28-day follow-up visits.

n. Serum chemistry (to include amylase and lipase) and thyroid function parameters are detailed in Section 6.1.13. All samples will be analyzed by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. The samples are to be collected at screening, prior to IP administration as detailed in Section 6.7.7, and at the treatment discontinuation and 28-day follow-up visits.

o. A serum pregnancy test is to be completed during screening for all FCBP. A serum or urine pregnancy test (investigator's discretion) is to be performed within 72 hours before beginning treatment on Day 1 of every cycle in the treatment phase, at the treatment discontinuation visit and safety follow-up (Section 6.1.14). The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative. Pregnancy testing does not need to be repeated prior to Cycle 1 if the screening assessment was performed within 72 hours of the first dose of IP.

p. Bone marrow and peripheral blood samples are required prior to beginning IP and following every 2 cycles of treatment during the first 6 treatment cycles (ie, Cycle Day 28 [± 14 days]). Subjects who continue beyond Cycle 6 will undergo bone marrow examination following every 3 treatment cycles or when necessary to confirm suspected hematologic response or disease progression, and again upon treatment discontinuation (See Sections 6.1.15, and 6.8.1 for detail). Samples will be sent for cytogenetic analysis each time a bone marrow sample is collected. Bone marrow biopsy and aspirate are required during screening. Thereafter, only aspiration is necessary unless adequate aspirate cannot be obtained. Reports from all bone marrow and cytogenetics analyses performed from the time of MDS diagnosis should be obtained and submitted to the sponsor during screening whenever possible. "Unscheduled" sample collections are also permitted if a subject has disease progression.

q. Pharmacokinetic samples will be collected from approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected study sites. Instructions for IP dosing and PK sample collection time points are provided in Section 6.10.

r. IP should only be dispensed on Day 1 of each treatment cycle after all Day 1 procedures have been completed and all IP from the previous cycle is accounted for (where applicable). Only 1 cycle of IP will be dispensed to the subject on Day 1 of each cycle (Section 8.2.1). For FCBP subjects, a negative pregnancy test performed within 72 hours prior to IP administration must be documented.

s. CC-486 is scheduled to be taken on Day 1 to Day 21 of each cycle (Day -1 of Cycle 1 for PK sub-study subjects), unless there has been a dose or schedule modification due to toxicity. Subjects will self-administer CC-486 (Section 8.2.2). It is recommended that an antiemetic medication (eg, ondansetron) be taken 30 minutes prior to CC-486 administration during Cycle 1. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed.

t. IP accountability is not applicable on Day 1 of Cycle 1.

u. The type of blood product transfused, number of units, reason for transfusion, and date of transfusion is to be collected beginning on C1D1, until 90 days after the last dose of IP or until the last study visit, whichever occurs later (see Section 6.8.6).

v. International Working Group Response Assessment based on modified IWG criteria (Appendix F) is to be performed following every 2 cycles of treatment during the first 6 treatment cycles. Subjects who continue beyond Cycle 6 will have IWG response assessment following every 3 treatment cycles. The assessment must be performed prior to beginning Day 1 procedures for the subsequent treatment cycle (Cycle 3, 5, 7, 10, etc.). See Section 6.8.3.

w. An assessment of disease status must be performed at the end of Cycle 6, prior to starting Cycle 7, based on available clinical and laboratory evaluations.
- Subjects who meet re-treatment criteria (Section 8.2.5) can continue on to Cycle 7 and beyond and disease status will be re-assessed prior to beginning each new cycle of IP.
- Subjects who fail to meet re-treatment criteria at the end of Cycle 6 will be discontinued from protocol-prescribed therapy and enter the follow-up phase (Section 6.14).

Prior to discontinuing a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

[x.] Subjects will be followed for safety-related assessments for 28 days (90 days for durvalumab).

[y.] During the Extension Phase while continuing to receive oral azacitidine. See details for the EP in Appendix J.

6. PROCEDURES

All required study visits are described in Table 2 with an "X" indicating the procedures to be performed during a particular visit. All data obtained from these assessments must be present in the subject's source documentation. Unless otherwise noted, acceptable study visit windows are as follows: routine assessments of Cycles 1 and 2 must be performed ± 3 days of the targeted day indicated in the table; all routine assessments of Cycles 3 and beyond must be performed ± 7 days of the targeted day; post-treatment follow-up contacts must be performed within ± 14 days of the targeted day of contact. Procedures are described in detail below.

6.1. Screening

All screening procedures and assessments are performed during a subject's screening period in order to establish eligibility and to document relevant medical and demographic data (eg, medical history and prior/concomitant medications). Written informed consent must be obtained before any study-specific procedures are performed and any samples are collected for study-specific analysis. Per inclusion criterion number 5, there may not be more than 16 weeks between a subject's last dose of injectable HMA and the date of their informed consent signature. Also, there may not be less than 3 weeks between the subject's last dose of injectable HMA and the planned first dose of IP in this study (inclusion criterion number 6). Given this timeframe, subjects may begin screening after the last dose of prior injectable HMA.

Subject eligibility is established by the investigator by confirming all inclusion and exclusion criteria are satisfied. Documentation used to establish eligibility should be forwarded to the sponsor to ensure documentation is sufficient from a regulatory and quality perspective. The sponsor may contact the study site for additional information if there is any deficiency in the documentation provided. Failure to satisfy any entry criterion will preclude a subject from enrolment into the safety run-in or treatment phase of the study. Unless otherwise specified, screening assessments must take place, and eligible subjects enrolled in the study within 28 days after the date of informed consent signature. Refer to Section 6.2 for information to be collected for *screen failures:* screened subjects who do not meet inclusion/exclusion criteria during screening, or who are not enrolled in the treatment phase for any reason.

A subject who becomes a screen failure can be rescreened if it is reasonable to believe they will meet eligibility criteria during rescreening. Please note that if a subject is to be rescreened, they must reconsent to participation in the study by signing a new and current Informed Consent Document and the date of signature must again be within 16 weeks of the last dose of injectable HMA.

6.1.1. MDS Diagnosis, WHO and FAB Classifications and IPSS(-R) Risk Classification

MDS diagnosis, WHO classification (Appendix A), FAB classification (Appendix B), IPSS risk classification (Appendix C), and IPSS-R risk classification (Appendix D) will be established through documentation collected during screening.

- Morphological assessment: Pathology reports from each bone marrow examination (screening biopsy and/or aspirate) performed from the time of MDS diagnosis should be obtained and submitted to the sponsor for review whenever possible. Inability to

clearly establish the diagnosis of MDS and disease progression or stable disease (without HI) as the best response to treatment with an injectable hypomethylating agent may preclude the subject from entering the study.

- Cytogenetics: Reports from any cytogenetics analyses performed from the time of MDS diagnosis should be obtained and submitted to the sponsor for review whenever possible.
- Hematology: Reports from any hematologic analyses from the time of MDS diagnoses that are relevant to establishing the subject's eligibility or baseline disease state (PD vs. SD) should be obtained and submitted to the sponsor for review whenever possible.

All hematology and bone marrow pathology reports used to establish a subject's eligibility should be sent for sponsor review at least 48 hours ahead of the planned IP start date to allow time for any deficiencies in documentation to be addressed. This includes documentation of the subject's prior treatment with an adequate course of injectable HMA and prior blood product transfusion records (see Sections 6.1.3 and 6.1.4). A checklist will be provided to the site to assist in compiling all necessary documentation during screening.

Note: Any time subject-specific documentation is sent to the sponsor, all subject-identifying information must be redacted, and the subject's study-specific ID number added to the document.

6.1.2. Demographics and Medical History

The subject's date of birth, sex, race and ethnicity will be recorded on the appropriate CRF, as permitted by local regulations. Relevant medical history and current medical conditions, including those symptoms related to MDS (eg, anemia), must be recorded on the appropriate CRF at screening.

6.1.3. RBC and Platelet Transfusion History

Documentation of all red blood cell and platelet transfusions received by the subject within 8 weeks (56 days) prior to the first dose of IP should be gathered during the screening period, if possible, and recorded on the appropriate CRF. Transfusion data should include the type of transfusion, number of units, reason for, and date of transfusion. RBC transfusion data should include the hemoglobin concentration prior to transfusion and platelet transfusion data should include the pre-transfusion platelet value. It is important that all transfusions received by the subject during the 56 days leading to the first dose of IP are known and recorded, even when not all requested data are available.

6.1.4. Prior Medications and MDS Treatments

All prior and current medications, including, prescription, over-the-counter, and herbal preparations taken for any indication within the 4 weeks (28 days) prior to the first dose of IP will be recorded on the appropriate CRF.

All prior treatments for MDS will be recorded on the respective CRF(s) regardless of dates of treatment.

Documentation of the subject's prior treatment with an adequate course of injectable HMA (see inclusion criterion number 3) should be sent to the sponsor at least 48 hours ahead of the planned date of first dose to allow time for sponsor review prior to initiating IP. Failure to clearly establish refractory disease (no objective response of HI or better) during or following an adequate course of injectable HMA will preclude the subject from being enrolled into the study.

Per inclusion criterion number 5, the last dose of injectable HMA must have been within 16 weeks prior to the subject's informed consent signature date in order to be considered for this study. Also, there may not be less than 3 weeks between the subject's last dose of injectable HMA and the planned first dose of IP in this study (inclusion criterion number 6).

6.1.5. Coagulation Parameters

Coagulation parameters, including prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), and fibrinogen will be recorded during screening. Re-testing of coagulation parameters throughout the study is only necessary if clinically indicated.

6.1.6. Physical Examination

Information about the screening physical examination must be present in the subject's source documentation. Significant findings will be recorded on the appropriate CRF.

6.1.7. Vital Signs, Body Weight and Height Measurements

The following routine assessments must be present in the subject's source documentation and recorded on the appropriate CRF:

- blood pressure
- pulse
- body temperature
- respiratory rate
- body weight

Height is collected during screening only.

6.1.8. Eastern Cooperative Oncology Group Performance Status

Performance status at screening will be assessed using ECOG criteria provided in Appendix E. Refer to Section 6.7.10 for timing of ECOG performance status assessments during the study.

6.1.9. Electrocardiogram

Electrocardiograms (ECGs) at screening and at treatment discontinuation are conducted locally. Electrocardiograms should be performed using the internationally recognized 12-leads. The investigator will review the results and assess as normal, abnormal - not clinically significant, or abnormal - clinically significant, and report abnormal finding(s) on the appropriate CRF. If the ECG is abnormal, the investigator should consult a cardiologist as appropriate. For purposes of

this study, ECGs will only be performed during screening and upon treatment discontinuation unless additional monitoring is deemed necessary by the investigator.

6.1.10. Urinalysis

During screening, a urine sample will be sent for analysis by the central laboratory. Urinalysis includes examination by a standard stick test for specific gravity, glucose, ketones, blood, pH, and protein, and microscopic analysis if indicated. A urine sample should be collected prior to IP administration on Day 1 of every 3rd treatment cycle (ie, Cycles 3, 6, 9, etc.), at treatment discontinuation and safety follow-up and sent to the central lab for analysis. Specific requirements for urine sample collection, handling, and shipping are provided in the Central Laboratory Manual.

6.1.11. Serum EPO, Ferritin, and Transferrin Saturation (Fe/TIBC)

Serum erythropoietin (EPO), ferritin, and serum iron/serum total iron-binding capacity (Fe/TIBC) are assessed by the central laboratory during screening to rule-out confounding conditions associated with anemia. It is not necessary to perform these tests if these parameters were assessed within 2 months prior to screening (date of informed consent signature) and values are documented in the subject's medical record.

6.1.12. Hematology

Blood samples for hematology assessment will be sent for analysis by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Refer to Section 6.7.7 for timing of required hematology assessments during the safety run-in or treatment phase of the study. Complete blood count (CBC) for hematology assessment includes:

- RBC count
- hemoglobin
- hematocrit
- reticulocyte
- mean corpuscular volume (MCV)
- red cell distribution width (RDW)
- platelet count
- White blood cell (WBC) count with differential
  - absolute and percent neutrophils
  - absolute and percent lymphocytes
  - absolute and percent monocytes
  - absolute and percent eosinophils
  - absolute and percent basophils
  - percent blasts

Specific requirements for blood sample collection, handling, and shipping are provided in the Central Laboratory Manual.

6.1.13. Serum Chemistry and Thyroid Function Tests

Samples for serum chemistry assessment will be sent for analysis by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Refer to Section 6.7.7 for timing of required serum chemistry assessments during the study. Serum chemistry assessments include:

- sodium
- potassium
- chloride
- bicarbonate (if available)
- calcium
- magnesium
- phosphorus
- uric acid
- total and direct/indirect bilirubin
- aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT)
- blood urea nitrogen (BUN)
- creatinine
- glucose
- albumin
- total protein
- alkaline phosphatase
- lactate deyhydrogenase (LDH)
- alanine aminotransaminase (ALT)/serum glutamate pyruvate transaminase (SGPT)
- thyroid stimulating hormone (TSH), free T4, free T3
- amylase
- lipase

Specific requirements for serum sample collection, handling, and shipping are provided in the Central Laboratory Manual.

6.1.14. Pregnancy Testing (FCBP Only)

This protocol defines a FCBP as a sexually mature woman who:

1. has not undergone a hysterectomy or bilateral oophorectomy, or
2. has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Amenorrhea following cancer therapy does not rule out childbearing potential.

The investigator will appraise a female subject as a FCBP according to this definition. Justification must be recorded in the CRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

A medically supervised serum pregnancy test with sensitivity of at least 25 mIU/mL is to be administered and assessed locally during screening for any FCBP. A negative result must be verified by the investigator prior to administration of IP. Refer to Section 6.7.8 for details

regarding pregnancy testing during the safety run-in and treatment phases of the study and to inclusion criterion numbers 8 and 9 for contraception requirements of the protocol.

6.1.15. Bone Marrow Aspirate, Biopsy, and Peripheral Blood Smear

A bone marrow aspirate and biopsy are to be obtained during screening. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared as well. Bone marrow and peripheral blood samples are then required following every 2 cycles of treatment during the first 6 treatment cycles (ie, Cycle Day 28 [± 14 days]). Subjects who continue beyond Cycle 6 will undergo bone marrow examination following every 3 treatment cycles or when necessary to confirm suspected hematologic response or disease progression, and again upon treatment discontinuation. Samples will be sent for cytogenetic analysis each time a bone marrow sample is collected. Bone marrow biopsy and aspirate are required during screening. Thereafter, only aspiration is necessary unless adequate aspirate cannot be obtained.

Samples will be processed as described in the Central Laboratory Manual and submitted for central review along with any pertinent clinical information. If documentation of MDS diagnosis, WHO/FAB classification and IPSS/IPSS-R risk categorization is available within 2 months of screening, results of central review are not required prior to enrollment of the subject in the study.

Instructions for submission of blood and bone marrow slides/samples, along with relevant clinical information, for central review are provided in the Central Laboratory Manual. Samples and documentation should be prepared and sent to the central reviewer as early in the screening process as possible, and not more than 3 weeks after the subject signs informed consent; this will enable resolution of any issues prior to the subject being enrolled into the study. Therefore, the informed consent process and screening procedures (including bone marrow collection) should be planned with careful consideration for the 28-day screening period to avoid any potential need for re-screening due to exceeding the 28-day limit. Special handling requests such as return of materials to the site will be managed on an individual basis.

6.1.16. Cytogenetics

Bone marrow cytogenetic testing will be completed by the central laboratory whenever a bone marrow aspirate (or biopsy) is obtained. Note that specific handling of the sample is required in order to be used for cytogenetics testing. See the Central Laboratory Manual for handling instructions.

6.2. Information to be Collected on Screen Failures

The following must be collected for all subjects who provide informed consent, but fail to satisfy inclusion criteria, or for any other reason, are not enrolled in the treatment phase of the study:

- informed consent date;
- date of biomarker sample collection;
- date of any request for biomarker sample destruction received from a subject;
- demographics;
- reason subject did not qualify for the study;

- investigator's signature

Any adverse events experienced by a screen failure subject will be collected from the date of signing informed consent to the day the subject is declared a screen failure. This information will be captured in the subject's source documents and appropriate CRF(s). Relevant information will also be recorded on a Screening Log. Subjects can be re-screened following discussion with the medical monitor.

6.3. Entering a Subject Into the Study (Enrollment)

Written consent must be obtained prior to any study-specific procedures being conducted. All the screening evaluations must be completed and eligibility criteria must be verified by the responsible investigator and appropriate documentation reviewed by the sponsor *prior* to enrolling a subject. Enrollment will occur via IRTS to enable automated tracking and replenishment of IP. Specific contact information and instructions will be provided to each study site.

The IRTS enrollment call should be performed as close as possible to the planned first dose of IP to avoid enrolling a subject who ultimately does not receive IP for any reason.

The first dose of IP should be administered at the site on the day of enrollment whenever possible, but may be delayed for up to 5 days if necessary for logistical reasons. Any delay greater than 5 days must be discussed with and approved by the sponsor's medical monitor, and may result in the need to repeat screening.

Subjects enrolled in the safety run-in phase of the study will be assigned to the monotherapy arm or the combination therapy arm. Subjects enrolled in the treatment phase of the study will be randomly assigned to one of the two treatment arms, while controlling for the numbers of subjects with PD and SD required in each arm for the planned analysis.

Approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected sites will participate in PK sampling procedures. Subjects participating in PK sample collection will have their first dose of CC-486 on Day -1 of Cycle 1, after collection of required samples on that day. See Section 6.10 for details.

6.4. Baseline Measurements

Baseline values are defined as the last assessment of a particular parameter (eg, vital signs, weight, or laboratory assessments) prior to administration of the subject's first dose of IP, unless noted otherwise for a particular assessment. In most cases, baseline assessments are those performed before dosing on Cycle 1, Day 1.

Baseline physical examination, ECOG performance status, hematology and/or serum chemistry do not need to be repeated prior to dosing if the screening examination was performed within 7 days of the first dose of IP and all necessary parameters were assessed.

6.5. CC-486 (Oral Azacitidine)

All eligible subjects will receive treatment with CC-486 at the dose and schedule identified during the safety run-in. Dose and schedule may be decreased as described in Section 8.2.4 in order to manage toxicity. In the absence of unacceptable toxicity, subjects who show signs of worsening

disease (clinical or hematological), who remain in stable disease, or do not experience modified IWG 2006 hematologic improvement (HI) or better (PR, CR or marrow CR – modified IWG 2006, Appendix F) after 2 well-tolerated cycles, may have their **dose increased** at the discretion of the investigator and in discussion with the medical monitor as defined in Table 3. Again, dose and schedule may be adjusted as described in Section 8.2.4 in order to manage toxicity.

After at least 2 treatment cycles at the increased dose, the assigned dose can be further increased if it is well-tolerated but no objective response is observed.

Special attention should always be given to potential drug-related toxicity and/or tolerability issues so dose and/or schedule can be reduced appropriately (Section 8.2.4).

Subjects can continue treatment with CC-486 as long as all protocol-specified re-treatment criteria continue to be met (see Section 8.2.5).

Best supportive care should be used in combination with study treatment as deemed necessary. Best supportive care includes, but is not limited to, treatment with RBC transfusions (pRBC or whole blood), single donor or pooled donor platelet transfusions, antibiotic, antiviral and/or antifungal therapy, antiemetic and/or antidiarrheal support, nutritional support as needed, and granulocyte (or granulocyte macrophage) colony-stimulating factors for subjects experiencing neutropenic fever or infection, and may be given as secondary prophylaxis (Section 9.1). Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors, except as noted for G- or GM-CSF in Section 9.1. It is recommended that an antiemetic medication such as ondansetron or an appropriate locally-available equivalent be taken 30 minutes prior to CC-486 administration during Cycle 1 of the treatment phase. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed.

Refer to Section 8.2 for details regarding IP dispensation, administration, and accountability.

6.6. Durvalumab (MEDI4736)

Subjects assigned to the combination treatment arm will receive durvalumab 1500 mg by 1-hour (± 5 minutes) IV infusion on Day 1 of each 28-day treatment cycle. Guidance for management of toxicity that is determined by the investigator to be related to treatment with durvalumab is provided in Section 8.2.4.2. Durvalumab dosing may be delayed until resolution of toxicity, but dose reductions for durvalumab are not permitted.

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

Site to supply the following:

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

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

Refer to Section 8.2 for details regarding IP dispensation, administration, and accountability.

6.6.1. Durvalumab Infusion Monitoring

Subjects will be monitored during and after infusion of durvalumab. Vital signs will be measured:

- prior to durvalumab administration (± 30 minutes),
- every 15 minutes (± 5 minutes) during durvalumab administration,
- at the end of durvalumab infusion (± 5 minutes),
- 30 minutes (± 5 minutes) post-infusion,
- 60 minutes (± 5 minutes) post infusion

followed by a 2-hour (± 15 minutes) period of observation.

6.7. Safety

Safety assessments include:

- AEs including AESI
- post-infusion monitoring for infusion- or immune-mediated AEs
- physical examination
- vital signs
- body weight
- ECOG performance status
- hematology (CBC with WBC differential and platelets – see Section 6.1.12)
- serum chemistry (to include amylase and lipase) and thyroid function tests (see Section 6.1.13)
- concomitant medications, therapies and procedures
- pregnancy testing (for FCBP subjects)
- urinalysis
- ECG
- coagulation parameters

6.7.1. Adverse Events

All subjects will be monitored for AEs including AESIs during the study. Refer to Section 11 for details regarding monitoring, recording, and reporting of AEs, including serious adverse events (SAEs) and AESIs.

Information about common side effects already known about azacitidine and durvalumab will be included in the subject informed consent document and should be discussed with the subject as needed during the study. This information can also be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of investigator notifications.

6.7.2. Progression to AML

Progression to AML will be monitored as an AESI and will be included as part of the safety assessment throughout the course of the study. Progression to AML should be reported if documented at any time from signing of informed consent through death, loss to follow-up, withdrawal of consent for further data collection, or study closure, whether or not thought to be related to treatment with IP.

Events of disease progression to AML are reported in the same way as SAEs using the seriousness criterion of "important medical event" if no other seriousness criteria apply. This information must also be documented on the appropriate CRFs and in the subject's source documents. Documentation supporting the diagnosis of progression to AML (eg, confirmatory histology or cytology results, etc.) must be provided at the time of reporting as an SAE. Refer to Section 11.2 for evaluation of AEs.

6.7.3. Physical Examination, Vital Signs and Weight

Physical examinations, vital signs (blood pressure, pulse, temperature, and respiratory rate) and weight measurements are to be performed as specified in Table 2. Significant findings must be included on the appropriate CRF.

6.7.4. Urinalysis

A urine sample obtained during screening and at the frequency specified in Table 2 will be submitted for analysis to the central laboratory according to the procedure detailed in the Central Laboratory Manual.

6.7.5. 12-Lead Electrocardiogram

A standard 12-lead ECG is to be performed during screening, upon treatment discontinuation, and whenever clinically indicated.

Electrocardiograms will be conducted locally as described in Section 6.1.9.

6.7.6. Coagulation Parameters

Coagulation parameters, including PT/INR, aPTT, and fibrinogen will be recorded during screening. Re-testing of coagulation parameters throughout the study is only necessary if clinically indicated.

6.7.7. Hematology and Serum Chemistry Laboratory Evaluations

Hematology and serum chemistry central laboratory analyses, including thyroid function tests, are to be performed according to the schedule in Table 2. The same parameters assessed during screening are to be evaluated throughout the treatment period, upon treatment discontinuation and at the 28-day follow-up visit (see Section 6.1 for details).

Samples for hematology analysis will be collected prior to IP administration on Day 1 of each treatment cycle and prior to IP administration on other required days, when possible. Samples will be processed as detailed in the study laboratory manual and sent to the central laboratory for analysis and reporting. The schedule of hematology assessments for enrolled subjects is as follows:

- Cycles 1-2 – Days 1, 8, 15 and 22
- Cycles 3-12 – Days 1 and 15
- Cycles ≥ 13 – Day 1
- Treatment Discontinuation Visit
- 28-day Follow-up Visit

Samples for serum chemistry analysis will be collected prior to IP administration on Day 1 of each treatment cycle and prior to IP administration on other required days during the first 2 cycles of treatment, if possible. Samples will be processed as detailed in the study laboratory manual and sent to the central laboratory for analysis and reporting. The schedule of serum chemistry assessments for enrolled subjects is as follows:

- Cycles 1-2 – Days 1, 8, 15 and 22
- Cycles ≥3 – Day 1
- Treatment Discontinuation Visit
- 28-day Follow-up Visit

Any or all laboratory assessments may be repeated more frequently if clinically indicated. In the event that an immediate laboratory assessment is required to acutely manage a subject, local laboratory tests may be used. In addition to collecting the local laboratory sample, a second sample should be processed for shipment to the central laboratory. If the subject management decision made based on the local laboratory result differs from the decision which the central lab result would have resulted in (when available), the applicable local laboratory result(s) should be recorded in the appropriate CRF.

Refer to Section 11.3 for guidance on the reporting of abnormal laboratory values and test results as AEs.

6.7.8. Pregnancy Testing

For all female subjects of childbearing potential (FCBP – see Section 6.1.14), a serum or urine pregnancy test (investigator's discretion) is required within 72 hours prior to beginning treatment in the study. The screening serum pregnancy test can be used to satisfy this requirement if it is performed within 72 hours prior to the first dose of IP.

A serum or urine pregnancy test (investigator's discretion) is to be done within 72 hours prior to dosing on Day 1 of every treatment cycle and at the treatment discontinuation and safety follow-up visits.

The subject may not receive IP until the investigator has verified that the result of a pregnancy test is negative.

Guidance for pregnancy testing during screening is provided in Section 6.1.14.

6.7.9. Concomitant Medications/Significant Non-drug Therapies/Concomitant Procedures

All prescription, over-the-counter, or herbal medications and therapeutic procedures received within 4 weeks (28 days) prior to the first dose of IP, until 28 days after the last dose of CC-486 and 90 days after durvalumab (or until the treatment discontinuation visit, whichever period is longer) must be recorded on the appropriate CRF page. Concomitant medications, therapies, and procedures are those that are received by the subject during their participation in the treatment phase of the study. If a medication, therapy, or procedure ended or was stopped prior to the first dose of IP, it will be recorded as a prior medication or as a part of the subject's medical history, as appropriate. See Section 9 for details regarding concomitant medications and procedures.

6.7.10. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Appendix E) is to be assessed during screening, before IP dispensation on Day 1 of each treatment cycle and at the treatment discontinuation and 28-day follow-up visits.

6.8. Efficacy

6.8.1. Bone Marrow Aspirate, Biopsy and Peripheral Blood Smear

During study treatment, bone marrow aspirate (or biopsy if adequate aspirate cannot be obtained) is collected:

- after completion of dosing in Cycle 2, Cycle 4, and Cycle 6,
- then after completion of dosing in every 3rd treatment cycle (9, 12, 15, etc.),
- to confirm suspected disease response or progression, and
- upon treatment discontinuation.

This sample, along with peripheral blood and blood smear slide(s) must be collected after the last dose of IP for that cycle, but before Day 1 of the next cycle. Samples will be processed according to instructions provided in the Central Laboratory Manual and sent for:

- central pathology review,
- central cytogenetics analysis, and
- CCI [redacted]

Results from central pathology review of blood and bone marrow samples will be used for:

- modified IWG response assessment,
- general disease status assessment, and
- monitoring for progression to AML.

Whenever a bone marrow sample is collected, a peripheral blood sample and peripheral blood smear is to be prepared as well. Specific requirements for submission of bone marrow samples for central review are detailed in the Central Laboratory Manual.

6.8.2. Cytogenetics

Bone marrow cytogenetic testing is to be completed by the central pathology laboratory whenever a bone marrow aspirate or biopsy is collected for disease assessment. Note that specific handling of the biopsy is required in order to be used for cytogenetics testing. See the Central Laboratory Manual for handling instructions.

6.8.3. International Working Group Modified Response Assessment

Hematologic response or improvement according to criteria modified from that of the International Working Group (IWG) (Appendix F) is to be assessed following every 2 treatment cycles during the first 6 months of treatment. Subjects who continue treatment will have IWG assessment repeated after every 3 cycles and at treatment discontinuation.

Due to the turnaround time required to obtain results from review of bone marrow aspirate and/or biopsy, peripheral blood smear and cytogenetics, IWG response assessment may be done at any time prior to starting the next cycle of treatment. Decisions regarding dose-modification and treatment continuation following IWG response assessment may be made based on available local assessments, if necessary, ahead of central hematology and bone marrow pathology assessments becoming available. However, after at least 6 cycles of treatment with IP, if central pathology assessment conveys disease progression, the subject must be notified as soon as possible (not later than the next scheduled study visit) to discontinue further study treatment and to schedule the treatment discontinuation visit, as appropriate.

6.8.4. General Disease Status Assessment

A general assessment of disease status must be performed at the completion of Cycle 6, prior to treatment in Cycle 7, based on available clinical and laboratory assessments.

- Subjects who meet any one of the following criteria can continue on to Cycle 7 and beyond, and will have disease status re-assessed prior to beginning each new cycle of IP based on available clinical and laboratory evaluations and at treatment discontinuation. Bone marrow examination will only be performed after Cycles 2, 4, 6, and every 3 cycles thereafter, as described in Section 6.8.1 above, unless additional bone marrow examination is deemed necessary by the investigator:
  - Objective response to treatment: CR, mCR, PR, or HI (Appendix F), or
  - RBC-transfusion-independence, or

  - ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
  - any other clinical benefit, including no evidence of progressive disease (see Table 8 for definitions of progressive disease).

  Thereafter, subjects may be discontinued from protocol-prescribed therapy for any of the reasons detailed in Section 12.

- Subjects who fail to meet these criteria at the end of Cycle 6 will be discontinued from protocol-prescribed therapy and enter the follow-up phase.

Prior to discontinuing a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

Confirmation of an RBC-transfusion-independent response requires that the investigator documents the dates, numbers of units, reason for transfusion, and pre-transfusion hemoglobin levels for all RBC transfusions received by the subject throughout the study in the subject's medical record. This will be compared to the subject's RBC transfusion history over the 56 days leading to enrollment, as recorded in the appropriate CRFs during screening.

In the event that immediate hematology values are needed for general disease status assessment prior to beginning a subsequent treatment cycle, local laboratory results may be used pending the outcome of the central laboratory assessment. However, matching samples must always be sent to the central laboratory and clinical decisions and assessments (such as General Disease Status Assessment) must be reconciled with the results of the central laboratory. Tests not required per-protocol, and not related to the conduct of the study, do not need to be duplicated by the central lab.

6.8.5. Hematology

Hematology results obtained from the central lab will be used to monitor subject safety and evaluate response to treatment.

In the event that immediate hematology values are needed for clinical decisions, local laboratory results may be used pending the outcome of the central laboratory assessment. However, matching samples must always be sent to the central laboratory and clinical decisions and assessments (such as continuation of treatment beyond Cycle 6) must be reconciled with the results of the central laboratory.

See Section 6.1.12 for a list of hematology parameters being assessed by the central laboratory for this study.

6.8.6. Transfusion Assessment

The following will be recorded for all transfusions the subject received within 56 days (8 weeks) prior to the first dose of IP, until 90 days after the last dose of CC-486 or durvalumab or the treatment discontinuation visit, whichever occurs later:

- type of transfusion (eg, pRBC or platelet)
- number of units
- reason for transfusion
- date of transfusion
- hemoglobin value for which any RBC transfusion is given
- platelet value for which any platelet transfusion is given

RBC transfusions administered for surgical procedures, significant hemorrhagic events, or other reasons documented as unrelated to MDS-associated anemia will not be counted in the assessment of baseline RBC transfusion requirements, efficacy, or progressive disease status.

RBC-transfusion-independent response or improvement will be assessed according to criteria modified from that of the International Working Group (Appendix F).

6.8.7. Survival, Progression to AML, and Subsequent MDS Therapies

All subjects discontinued from protocol-prescribed therapy for any reason should undergo treatment discontinuation procedures (Section 6.13) and be followed for survival, disease progression to AML, and subsequent MDS therapies (Section 6.14). Data regarding subsequent therapies, determination of disease progression, and date and cause of death will be recorded in the appropriate CRF.

6.9. Biomarkers

Subjects participating in this study must consent to the future use of bone marrow and blood samples collected during screening, throughout treatment, and upon treatment discontinuation for biomarker analyses. Screening samples may be obtained at any point after signing the informed consent document, up until taking the first dose of IP.

Saliva, whole blood, and bone marrow aspirate and biopsy samples will be collected and analyzed at the following time points to evaluate protein, nucleic acid and cellular biomarkers that relate to durvalumab treatment.

Saliva sample for biomarkers will be collected at screening.

Blood samples for biomarkers will be collected at the following time points:

- Screening for sPD-L1, soluble factors, immunophenotyping, peripheral blood mononuclear cells (PBMCs)
- C1D1 (predose) for sPD-L1, soluble factors, immunophenotyping, whole blood DNA
- C1D8 (predose) for soluble factors, immunophenotyping
- C1D15 (predose) for soluble factors, immunophenotyping
- C2D1 (predose) for sPD-L1, soluble factors, immunophenotyping, whole blood DNA
- C2D15 (predose) for soluble factors, immunophenotyping
- C3D15 (predose) for soluble factors, PBMCs

- C4D15 (predose) for soluble factors
- C5D1 (predose) and every 3 cycles thereafter (C8D1, C11D1 etc.) sPD-L1, PBMCs
- EOT (predose) for soluble factors, whole blood DNA, PBMCs

CCI [redacted]

Planned bone marrow sampling will be performed:

- during screening,
- after the completion of dosing in Cycle 2, Cycle 4, and Cycle 6,
- then after the completion of dosing in every 3rd treatment cycle (9, 12, 15, etc.),
- to confirm suspected disease response or progression, and
- upon treatment discontinuation.

as indicated in the Table of Events (Section 5).

Peripheral blood samples for future biomarker analyses should be collected on the same day as the screening bone marrow biopsy procedure. If samples for biomarker assessment are not collected in conjunction with other screening procedures, or are in any way unfit for analysis, the sample may be obtained on Day 1, prior to IP administration.

Consent for biomarker sampling procedures will be obtained through signature of a biomarker-specific component of the informed consent document. All subjects participating in this study will consent to biomarker sampling procedures, as described.

CCI [redacted]

6.10. Pharmacokinetics

Blood samples for pharmacokinetic analysis will be collected from approximately 10-12 evaluable subjects randomized to the combination treatment arm at selected sites. This will enable assessment of drug-drug interactions. Subjects will receive CC-486 approximately one hour after completion of the durvalumab infusion except on Day -1.

Subjects participating in PK procedures will agree to have blood samples collected as described below (see also Section 8.2.2).

- Dosing for subjects participating in PK procedures:
  - Cycle 1:
    - CC-486: established Phase 2 dose on Day (-1) and Days 2 to 21 of a 28-day cycle
    - Durvalumab: on Day 1, 1500 mg administered IV over a 1-hour period (± 5 minutes)
  - Cycle 2:
    - CC-486: established Phase 2 dose on Day 1 to 21 of a 28-day cycle
    - Durvalumab: on Day 1, 1500 mg administered IV over a 1-hour (± 5 minutes) period
- PK sample collection timepoints:
  - CC-486:
    - Cycle 1 Day (-1): predose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose
    - Cycle 2 Day 1: predose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose

    Prior to each CC-486 PK sampling day, subjects must fast overnight (refer to Section 8.2.2.1 for fasting details).
  - Durvalumab:
    - Cycle 1 Day 1: pre-infusion (-30 to -5 minutes prior to dose), end of infusion (EOI), 2 hours (± 1 hour), 8 hours (± 1 hour), 48 hours (C1D3) (± 2 hour), 168 hours (C1D8) (± 2 hour), 336 hours (C1D15) (± 2 hour) and 504 hours (C1D22) (± 2 hour) after administration of durvalumab on C1D1
    - Cycle 2 Day 1: pre-infusion (-30 to -5 minutes prior to dose), end of infusion (EOI), 2 hours (± 1 hour), 8 hours (± 1 hour), 48 hours (C2D3) (± 2 hour), 168 hours (C2D8) (± 2 hour), 336 hours (C2D15) (± 2 hour) and 504 hours (C2D22) (± 2 hour) after administration of durvalumab on C2D1
    - PK samples collected at the following timepoint to match immunogenicity sample collections: Cycle 4 Day 1, Cycle 6 Day 1, Cycle 10 Day 1, and Cycle 14 Day 1: pre-infusion (-30 to -5 minutes prior to dose)

NOTE: for immunogenicity, samples should be collected from all subjects dosed with durvalumab, CCI [redacted]. Samples will be stored and ADA assessment will be explored.

6.11. Immunogenicity Samples of Durvalumab

Immunogenicity samples will be collected as follows:

- Pre-dose samples on C1D1, C2D1, C4D1, C6D1, C10D1 and C14D1.

NOTE: for immunogenicity, samples should be collected from all subjects dosed with durvalumab, CCI [redacted]. Samples will be stored and ADA assessment will be explored.

6.12. Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests, vital signs, etc.) outside of scheduled study visits, the results of the repeat evaluation should be recorded in an *unscheduled visit* CRF. These evaluations should also appear in the subject's chart and/or other source documentation.

6.13. Discontinuation

Prior to discontinuing a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

All subjects who have received at least one dose of IP should undergo *treatment discontinuation* procedures when IP is discontinued, including:

- AEs including AESI
- physical examination
- electrocardiogram
- vital signs
- body weight
- ECOG performance status
- hematology
- serum chemistry (to include amylase and lipase) and thyroid function tests
- urinalysis
- pregnancy test (FCBP only)
- concomitant medications, therapies and procedures
- transfusion assessment
- bone marrow aspirate/biopsy and peripheral blood smear
- whole blood sample for biomarker analysis
- cytogenetics

- IWG response assessment
- general disease status assessment
- IP accountability
- Subsequent MDS therapies (following IP discontinuation, if applicable)

If a subject is discontinued during a regularly scheduled visit, all treatment discontinuation procedures should be completed at that visit. If a procedure had been performed within 7 days of the treatment discontinuation visit, it does not need to be repeated.

The reason for discontinuation will be recorded in the CRF and in source documents for all enrolled subjects, whether or not they ever received a dose of IP. Guidance for reporting of reasons for discontinuation is provided in Section 12.

In the event that a subject assigned to the combination treatment arm discontinues treatment with durvalumab or CC-486 because of drug-related toxicity, treatment with single-agent durvalumab or CC-486 may continue until any discontinuation criterion is met (see Section 12).

6.14. Follow-up

All subjects discontinued from treatment with IP for any reason will be followed for a period of at least 28 days after the last dose of CC-486 (90 days for durvalumab) or until the date of the treatment discontinuation visit, whichever is later. During *Safety Follow-up Visits*, the following assessments will be performed:

- AEs including AESIs (monitored until 28 days after last dose of CC-486 or 90 days after last dose of durvalumab, whichever date is later)
- physical examination
- vital signs
- body weight
- ECOG performance status
- hematology
- serum chemistry (to include amylase and lipase) and thyroid function tests
- pregnancy testing (FCBP only)
- urinalysis
- concomitant medications, therapies and procedures
- transfusion assessment
- subsequent MDS therapies

Females of childbearing potential should avoid becoming pregnant for at least 90 days after the last dose of IP and male subjects should avoid fathering a child for at least 90 days after the last dose of IP. The ICF will address any country-specific requirements, as needed.

All subjects discontinued from protocol-prescribed therapy for any reason will also be contacted by telephone every 3 months (12 weeks ± 14 days) following the treatment discontinuation visit until the last active subject reaches 12 months of treatment, or until death, loss to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to:

- survival
- subsequent MDS therapies
- disease progression to AML

The investigator must make every effort to obtain information regarding the subject's follow-up status. All attempts to contact the subject must be documented and appropriate due diligence must be demonstrated before the subject can be considered lost to follow-up (eg, 3 unsuccessful attempts by telephone and one unanswered written attempt sent by certified or traceable post).

6.15. Extension Phase

During the Extension Phase, ongoing subjects will continue to receive oral azacitidine. See details for the EP in Appendix J.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This multi-center, international study will enroll at least 70 to 194 evaluable subjects (inclusive of subjects in the safety run-in and randomized phases).

At least 6 evaluable subjects will be included in the safety run-in phase of the study: 3 receiving monotherapy, and 3 receiving combination therapy.

During the randomized treatment phase of the study, approximately 32 subjects with PD and 32 subjects with SD will be randomized evenly to receive either CC-486 alone, or CC-486 + durvalumab. There will be 4 cohorts (16 subjects in each) in Stage 1: SD treated with monotherapy, PD treated with monotherapy, SD treated with combination therapy and PD treated with combination therapy.

If there are 2 or fewer responses in either cohort during Stage 1, enrollment to that cohort will be terminated. Otherwise, the cohort will continue to Stage 2 and accrue an additional 25 subjects each. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected for that cohort.

Therefore, the total number of subjects for the randomized treatment phase will range from approximately 64 (at Stage 1) to 164 (Stage 1 plus Stage 2) for the 4 cohorts. More subjects can potentially be recruited for replacement of non-evaluable subjects, if needed (see Figure 2).

The study population may include subjects with both lower- and higher-risk disease who meet the following criteria.

7.2. Inclusion Criteria

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

1. Male or female, ≥ 18 years of age at the time of signing the informed consent document
2. Documented diagnosis of MDS, classified according to FAB classification criteria (Appendix B)
3. Adequate course of treatment with an injectable hypomethylating agent (azacitidine for injection or decitabine) as the last therapeutic intervention for MDS prior to beginning screening for this study

   Adequate is defined as:

   - having received at least 6 consecutive 4-week treatment cycles with azacitidine for injection, or
   - having received at least 4 consecutive 6-week treatment cycles with decitabine (3-day regimen) or at least 6 consecutive 4-week treatment cycles with decitabine (5-day regimen), or
   - having demonstrated inability to tolerate treatment with an injectable hypomethylating agent because of unacceptable drug-related toxicity after at least

3 months of attempted treatment: Three 28-day cycles of azacitidine for injection or decitabine 5-day regimen; two 42-day cycles of decitabine 3-day regimen.

4. Documented *disease progression* or *stable disease* as best response to treatment (or attempted treatment) with azacitidine for injection or decitabine. Those achieving an objective response to treatment regimen with an injectable HMA (Appendix F) are excluded from participation in this study.

   Definitions of *disease progression* are modified from IWG 2006 criteria (Appendix F) and include:

   – Pre-injectable HMA baseline bone marrow myeloblasts:
     - Less than 5%: ≥ 100% increase to ≥ 8% blasts
     - ≥ 5%: ≥ 50% increase to ≥ 10% blasts

   Note: ≥ 30% blasts is considered AML per FAB classification. Subjects known to have ≥ 30% blasts are not eligible for inclusion in this study. Recognizing limitations of blast cell quantification, this protocol will allow subjects with pre-enrollment bone marrow blast counts up to 33% on the screening bone marrow examination to be considered for inclusion. Assessment may be made according to local bone marrow examination to facilitate enrollment of eligible subjects into the treatment phase of the study.

   – Any clinical worsening from pre-injectable HMA baseline condition, including:
     - sustained clinically-significant worsening (investigator's assessment) from baseline granulocyte, platelet, or hemoglobin values (≥ 2 values, separated by ≥ 2 weeks)
       - worsening granulocytes should be ≥ 50% decrease from pre-injectable HMA baseline value
       - worsening platelets should be ≥ 50% decrease from pre-injectable HMA baseline value (untransfused)
       - worsening hemoglobin should be ≥ 1.5 g/dL decrease from pre-injectable HMA baseline value in subjects not receiving RBC transfusions
     - meaningful worsening in RBC or platelet transfusion requirement

   Definition of *stable disease* is based on modified IWG 2006 criteria (Appendix F):

   – Failure to achieve any objective response (CR, PR, mCR, or HI), but no evidence of disease progression within the 8 weeks leading to the subject's first dose of IP in this study (Cycle 1, Day 1).

5. Have the last dose of the prior treatment regimen (injectable HMA – azacitidine for injection or decitabine) not more than 16 weeks prior to screening for this study (date of informed consent signature).
6. No less than 3 weeks between the last dose of the prior treatment regimen (injectable HMA – azacitidine for injection or decitabine) and the planned date of first dose of IP.

7. Have an ECOG performance status of 0, 1, or 2 (Appendix E)
8. Females subjects of childbearing potential[1] may participate, providing they meet the following conditions:
    a. Have two negative pregnancy tests as verified by the investigator prior to starting any IP therapy: serum pregnancy test at screening and negative serum or urine pregnancy test (investigator's discretion) within 72 hours prior to starting treatment with IP (Cycle 1, Day 1). They must agree to ongoing pregnancy testing during the course of the study (before beginning each subsequent cycle of treatment), and after the last dose of any IP. This applies even if the subject practices complete abstinence[2] from heterosexual contact.
    b. Agree to practice true abstinence[2] (which must be reviewed on a monthly basis and source documented) or agree to the use of highly effective methods of contraception from 28 days prior to starting durvalumab or azacitidine, and must agree to continue using such precautions while taking durvalumab or azacitidine (including dose interruptions) and for up to 90 days after the last dose of durvalumab or azacitidine. Cessation of contraception after this point should be discussed with a responsible physician.
    c. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of IP.
    d. Refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.

    Note that the screening serum pregnancy test can also be used as the test prior to starting IP if it is performed within the 72-hour timeframe.
9. Male subjects must:
    a. Either practice true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis) or agree to avoid fathering a child, to use highly effective methods of contraception, male condom plus spermicide during sexual contact with a pregnant female or a female of child bearing potential (even if he has undergone a successful vasectomy) from starting dose of IP (Cycle 1 Day 1), including dose interruptions through 90 days after receipt of the last dose of durvalumab or azacitidine.
    b. Refrain from semen or sperm donation while taking IP and for at least 90 days after the last dose of IP.
10. Understand and voluntarily sign an informed consent document prior to any study-related assessments or procedures conducted.

[1] A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).

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

11. Be able to adhere to the study visit schedule and other protocol requirements.
12. Understand and voluntarily sign a biomarker-specific component of the informed consent document prior to any study-related procedures conducted.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from participation in the study:

1. Rapidly-progressing MDS, defined as:
   a. Known clinically-significant doubling in marrow or peripheral blood blast percentage (to ≥ 20%) in the 8-week period leading to the first dose of IP (Cycle 1, Day 1) or
   b. ≥100% increase in WBC count (myeloid cell line and monocyte series) within the 8-week period leading to Cycle 1, Day 1
2. Acute myelogenous leukemia (AML – FAB classification: ≥ 30% blasts in bone marrow). Subjects known to have ≥ 30% blasts are not eligible for inclusion in this study. Recognizing limitations of blast cell quantification, this protocol will allow subjects with pre-enrollment (screening/baseline) bone marrow blast counts up to 33% to be considered for inclusion.
3. Prior allogeneic stem cell transplant
4. Prior exposure to the investigational oral formulation of decitabine, or other oral azacitidine derivative at any time in the subject's prior history
5. Prior or ongoing response (IWG 2006: HI, PR, CR, or marrow CR) to treatment with azacitidine for injection or decitabine, at any time in the subject's prior history, which includes relapsed disease
6. Ongoing medically significant adverse events from previous treatment, regardless of the time period
7. Use of any of the following within 28 days prior to the first dose of IP:
   a. thrombopoiesis-stimulating agents ([TSAs]; eg, Romiplostim, Eltrombopag, Interleukin-11)
   b. ESAs and other RBC hematopoietic growth factors (eg, interleukin-3)
   c. hydroxyurea
8. Concurrent use of corticosteroids unless the subject is on a stable or decreasing dose for ≥ 1 week prior to enrollment for medical conditions other than MDS
9. 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
10. Prior history of malignancies, other than MDS, unless the subject has been free of the disease for ≥ 3 years. However, subjects with the following history/concurrent conditions are allowed:

a. Basal or squamous cell carcinoma of the skin
b. Carcinoma in situ of the cervix
c. Carcinoma in situ of the breast
d. Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)

11. Significant active cardiac disease within the previous 6 months, including:
    a. New York Heart Association (NYHA) class IV congestive heart failure (see Appendix G);
    b. Unstable angina or angina requiring surgical or medical intervention; and/or
    c. Myocardial infarction
12. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
13. Known Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) infection, or evidence of active Hepatitis B Virus (HBV) infection
14. Any of the following laboratory abnormalities:
    a. Serum AST/SGOT or ALT/SGPT > 2.5 x ULN
    b. Serum total bilirubin > 1.5 x ULN. Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis). Subjects are excluded if there is evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count of > 2% with either a positive Coombs' test or over 50% of indirect bilirubin
    c. Serum creatinine > 2.5 x ULN
    d. Absolute WBC count $\geq 20 \times 10^9$/L
15. Known or suspected hypersensitivity to azacitidine, mannitol, or durvalumab, its constituents, or to any other humanized monoclonal antibody
16. Pregnant, planning to become pregnant starting from 28 days prior to receiving CC-486 or durvalumab, throughout your participation in the study, and for at least 90 days following your last dose of study treatment, or breast-feeding females
17. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
18. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
19. Any condition that confounds the ability to interpret data from the study, including known or suspected conditions other than MDS, associated with anemia
20. Having received any prior MAb against CTLA-4, PD-1, or PD-L1 or having received other investigational MAbs within 6 months
21. Clinical evidence of central nervous system (CNS) or pulmonary leukostasis, or CNS leukemia

22. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of durvalumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical or local steroid injections (eg, intra-articular injection);
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent;
    c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
23. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener's syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis; hypophysitis, uveitis; etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
    a. Subjects with vitiligo or alopecia;
    b. Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement for ≥ 3 months; or
    c. Subjects with psoriasis not requiring systemic treatment
24. History of primary immunodeficiency
25. Receipt of live, attenuated vaccine within 30 days prior to the first dose of durvalumab (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 30 days after the last dose of durvalumab)
26. Active myeloproliferative neoplasms (MPN) and chronic myelomonocytic leukemia (CMML)

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Investigational product supply will be managed by IRTS. All IP must be stored in accordance with the product label in a secured area to prevent unauthorized access.

8.1.1. CC-486 (Oral Azacitidine)

Celgene Corporation will supply CC-486 100-, 150-, and 200-mg tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products. A list of excipients included in the formulation is provided in the azacitidine IB.

After Amendment 4 approval, the CC-486 supply will be limited to 100-mg tablets for oral administration.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed.

Shelf-life evaluation of the intact blister card is ongoing. Investigational Product will be monitored for stability for the duration of the study.

8.1.2. Durvalumab (MEDI4736)

Durvalumab will be supplied by Celgene Corporation in single use vials in single count cartons. Each 10mL vial will be supplied as a vialed liquid solution containing 500 mg (nominal) of investigational product at a concentration of 50 mg/mL. Durvalumab is stored at 2°C - 8°C (36°F to 46°F) and must be used before the individually assigned expiry date on the label.

Durvalumab will no longer be supplied during the Extension Phase as no subjects are being treated with durvalumab.

8.2. Treatment Administration and Schedule

After the safety run-in is complete and the CC-486 dose and regimen to be used in combination with durvalumab is established, eligible subjects will be randomized to receive CC-486 alone or in combination with durvalumab in the randomized treatment phase of the study. All randomized subjects will receive CC-486 orally administered tablets at the established dose and schedule. The schedule will include BID dosing on days 1-21 of each 28-day treatment cycle. Subjects randomized to the combination therapy arm will receive durvalumab, 1500 mg on Day 1 of each 28-day treatment cycle by IV infusion over approximately 1 hour (± 5 minutes). CC-486 tablets should be ingested approximately 1 hour after completion of the durvalumab infusion on Day 1 of each treatment cycle (except for Cycle 1 in which CC-486 is given on Day -1 for PK sub-study subjects) as described in Section 8.2.2. In the event of unacceptable toxicity, CC-486 dose and schedule may be modified (see Section 8.2.4). Infusions of durvalumab may be interrupted, slowed, or discontinued in order to address toxicity, but dose reduction of durvalumab is not permitted (see Section 8.2.4.2).

In the absence of unacceptable toxicity, subjects who show signs of worsening disease (clinical or hematological), who remain in stable disease, or do not experience modified IWG 2006 hematologic improvement (HI) or better (PR, CR or marrow CR – modified IWG 2006, Appendix F) after 2 well-tolerated cycles, may have their **dose increased** at the discretion of the investigator and in discussion with the medical monitor as described in Section 8.2.4 and Table 3. Again, dose and schedule may be adjusted as described in Section 8.2.4 in order to manage toxicity.

Subjects may continue to receive the protocol-prescribed therapy for as long as they benefit from the treatment (Section 4.1.3) or until treatment is discontinued for reasons detailed in Section 12.

Prior to discontinuing a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. However, the decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

8.2.1. Investigational Product Dispensation

8.2.1.1. CC-486 Dispensation

CC-486 will be dispensed on Day 1 of each treatment cycle (except for Cycle 1 in which CC-486 is given on Day -1 for PK sub-study subjects).

Only 1 cycle of IP will be dispensed to the subject at this time unless extreme extenuating circumstances apply and other arrangements are agreed to by the sponsor's medical monitor in writing.

The subject may not receive IP for each treatment cycle until all Day 1 procedures have been completed and all IP from the previous cycle is accounted for (where applicable).

For FCBP subjects, a pregnancy test must be performed, and a negative result verified by the investigator, within 72 hours prior to IP administration on Day 1 of each treatment cycle.

8.2.1.2. Durvalumab Dispensation

Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours **at room** temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab does not contain preservatives and any unused portion must be discarded.

Sites should follow standard and local aseptic procedures and the clinical study protocol for all activities. All dispensing activities should be documented according to local procedures.

The shelf lives stated above are based on chemical and physical stability; assignment of microbial shelf life is the responsibility of the clinical center and should be aligned with local procedure for managing microbial risk as long as the times specified in this section are not exceeded. Vials should be used for the specific subjects to whom they are assigned, and must not be shared between subjects.

8.2.2. Investigational Product Administration

8.2.2.1. CC-486 Administration

Investigational product administration will be accurately recorded including, but not limited to, date of administration, dose and any changes in dose administration (eg, interruption or reduction in dose due to an adverse event).

Investigational product is scheduled to be taken on the first 21 days of each 28-day treatment cycle, unless there has been a schedule modification of CC-486 administration due to toxicity.

Subjects will be instructed to take CC-486 twice daily, in the morning and evening, at approximately the same times each day. It is recommended that an antiemetic medication be taken 30 minutes prior to CC-486 administration during Cycle 1. If nausea / vomiting is not significant, antiemetic prophylaxis may not be needed. Subject will ingest CC-486 tablets with approximately 240 mL (8 ounces) of room temperature water. Investigational product may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories can be provided as a guidance).

Subjects assigned to the combination treatment arm will take their first dose of CC-486 on Day 1 of each treatment cycle approximately one hour after completion of the durvalumab infusion. If an antiemetic medication is to be administered, it should be taken about 30 minutes prior to dosing with CC-486.

For subjects enrolled in the PK population, the treatment administration of the first dose of CC-486 on PK days (ie, Cycle 1 Day -1 and Cycle 2 Day 1) 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 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 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.

Dietary restrictions on PK days (ie, Cycle 1 Day -1 and Cycle 2 Day 1):

- 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 is administered. Water can be allowed as desired except for 1 hour before and after CC-486 administration. The only water permitted in the 1-hour period before CC-486 administration is the 240 mL of water for antiemetic ingestion.

On Cycle 2 Day 1, the first dose of CC-486 will be administered approximately one hour after the completion of the durvalumab infusion.

8.2.2.2. Durvalumab Administration

Preparation of durvalumab and preparation of the IV bag are to be performed aseptically. Vials should be used for the specific subjects to whom they are assigned, and must not be shared between subjects.

- Three (3) vials of durvalumab (500 mg/vial; 50 mg/mL) are used to prepare a single infusion of the per-protocol dose of 1500 mg.
- Vials containing durvalumab may be gently inverted for mixing, but should not be shaken. All durvalumab vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.

8.2.2.2.1. Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; they should not be prepared on the ward.

- A total of 30 mL durvalumab (contained in 3 vials) is added to an IV bag containing 250 mL normal saline (Section 6.6), supplied by the site. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.
- Following preparation of the dose, the entire contents of the IV bag should be administered.
- Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

8.2.2.2.2. Infusion schedule and rates

Durvalumab will be administered as a 1-hour (± 5 minutes) IV infusion on Day 1 of each 28-day treatment cycle.

8.2.2.2.3. Monitoring of dose administration

Subjects will be monitored during and after infusion of durvalumab. Vital signs will be measured within 30 minutes prior to durvalumab administration, every 15 minutes (± 5 minutes) during durvalumab administration, within 5 minutes of completing the durvalumab infusion, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion of durvalumab, followed by a 2-hour (± 15 minutes) period of observation.

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

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

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

8.2.3. Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each 28-day treatment cycle. Any missed doses of CC-486 during that period should not be taken after the last scheduled day of administration, but should be returned by the subject for IP accountability.

8.2.4. Dose Modifications and Toxicity Management

8.2.4.1. CC-486 (Oral Azacitidine) Dose Modification and Toxicity Management

All efforts should be made to maintain treatment with CC-486 according to schedule without cycle delay, dose interruption, or reduction. Subjects will be monitored for hematologic toxicity and non-hematologic toxicity with the NCI CTCAE Version 4.03 used as a guide for the grading of severity.

If adverse events are observed that are considered by the investigator to be at least possibly related to treatment, CC-486 dosing may be interrupted, delayed or modified. The investigator is encouraged to contact the medical monitor prior to any treatment adjustment, if possible.

For any adverse event that would put a subject at unacceptable risk in the investigator´s opinion (eg, Grade 4 neutropenia), CC-486 dosing may be interrupted, delayed or modified, even if not considered by the investigator to be at least possibly related to treatment.

A minimum CC-486 dose and schedule of 100 mg BID 14/28d (or 200 mg QD 14/28d) is permitted in the event of toxicity (see Table 3). Subjects who cannot tolerate this minimum dose and schedule should discontinue the treatment phase of the study and enter follow-up.

Subjects who have their CC-486 dose reduced or treatment schedule modified may return to their original dose and/or schedule in a stepwise fashion upon discussion and documented agreement between the investigator and the medical monitor, provided that at least two treatment cycles have proven tolerable at the current dose and schedule. The treatment schedule should first be increased from 14/28 days to 21/28 days at 100 mg BID (or 200 mg QD if the rescue dosing option was utilized), followed by a stepwise escalation in dose (eg, 100 mg BID to 150 mg BID or 200 mg QD to 300 mg QD, etc.). At least two treatment cycles without unacceptable drug-related toxicity should precede any increase in dose or schedule.

In the absence of unacceptable toxicity, subjects who show signs of worsening disease (clinical or hematological), who remain in stable disease, or do not experience modified IWG 2006 hematologic improvement (HI) or better (PR, CR or marrow CR – modified IWG 2006, Appendix F) after 2 well-tolerated cycles, may have their **dose increased** at the discretion of the investigator and in discussion with the medical monitor as described in Section 6.5 and Table 3. Again, dose and schedule may be adjusted as described in Section 8.2.4 in order to manage toxicity.

After Amendment 4 approval, dose increases will no longer be allowed. Dose decreases following Table 3 are still allowed. Subjects will continue at the same dose levels during the Extension Phase. Any potential dose escalation will be considered a treatment failure and the subject should be discontinued.

Refer to Section 8.2.5 if, despite temporary interruption, delay or modification of study treatment, the toxicity persists for more than 42 days and is considered by the investigator to be at least possibly related to study treatment.

Following any modification of study treatment or if a dose is missed, the subject should stay on the visit schedule as specified in Table 2. Unscheduled visits may occur to monitor the subject's toxicities if necessary.

Table 3: CC-486 Dose Modification Steps

Dose Modification Step	BID Dose and Schedule Days	Rescue Step	Rescue (QD) Dose and Schedule (Days)
+2	300 mg BID, 21/28		
+1	250 mg BID, 21/28		
0[a]	**200 mg BID, 21/28**		
-1	150 mg BID, 21/28	R+2	300 mg QD, 21/28
-2	100 mg BID, 21/28	R+1	200 mg QD, 21/28
-3[b]	100 mg BID, 14/28	Rescue (R)	200 mg QD, 14/28

BID = twice daily; QD = once daily; R = rescue dose step.
[a] Highest starting dose to be evaluated.
[b] Any subject who cannot tolerate dose modification Step -3 (or R) will discontinue IP and enter the follow-up period.
→ Dose adjustment options from current dose/regimen. Dose/schedule reduction does not need to be taken stepwise.

Dose Modification for Febrile Neutropenia

Any subject who experiences febrile neutropenia ≥ Grade 3 that persists for up to 3 days may, with concomitant antibiotic, antiviral, and/or antifungal therapy, continue to receive IP uninterrupted at the investigator's discretion. If the event exceeds 3 days, IP should be temporarily interrupted. Dose modification may be considered as summarized in Table 4.

Dose Modification for Neutropenia Grade 4

For subjects entering the study with pre-existing Neutropenia Grade 4, treatment should be started at the regular starting dose and schedule of 200 mg BID 21/28d. However, if neutropenia continues to worsen under treatment, dose modification may be considered as summarized in Table 4.

For any subject who experiences a worsening of neutropenia to Grade 4 for ≥ 4 days, independent of whether considered related to IP or not, a dose modification may be considered as summarized in Table 4.

Dose Modification for Diarrhea

It is recommended that subjects experiencing diarrhea be managed according to the guidelines provided in Appendix H. Anti-diarrhea medication may be administered as prophylaxis against diarrhea and for treatment of any adverse events of diarrhea. Recommended dose modification steps for diarrhea (≥ Grade 2) are summarized in Table 4. If further dose-reduction beyond modification Step -3 (or the QD *rescue* regimen) is thought to be necessary, IP should be discontinued and the treatment discontinuation visit scheduled.

Dose Modification for Nausea and Vomiting

A serotonin (5-HT_3) receptor antagonist (eg, ondansetron) or other comparable medication may be administered as an antiemetic prophylaxis approximately 30 minutes prior to IP administration if necessary. Antiemetic pretreatment is recommended during the first cycle of the treatment phase. If the subject does not experience significant nausea and/or vomiting, further use of antiemetic medications may not be necessary. Antiemetic medication(s) should be administered for treatment of any adverse events of nausea and/or vomiting. Recommended dose modifications for nausea and vomiting (≥ Grade 3) are summarized in Table 4. If further dose-reduction beyond modification Step -3 (or the QD *rescue* regimen) is thought to be necessary, IP should be discontinued and the treatment discontinuation visit scheduled.

Dose Modification for Renal Dysfunction and Abnormal Serum Electrolytes

If unexplained elevations of serum creatinine or electrolyte disturbances occur, dose or schedule modifications may be implemented as summarized in Table 4. If further dose-reduction beyond modification Step -3 (or the QD *rescue* regimen) is thought to be necessary, IP should be discontinued and the treatment discontinuation visit scheduled.

Dose Modification for Weight Change

No dose adjustment should be made for weight loss or gain alone; however, the reason for weight loss (eg, significant nausea, vomiting, anorexia, etc.) or weight gain (eg, peripheral edema) should be investigated and may require a dose modification as specified in Table 4.

Dose Modification for Any Other Adverse Event

Any subject who experiences any hematologic or non-hematologic adverse event ≥ Grade 2, that is a worsening from baseline state (see Section 6.4 for baseline definition) and would put a subject at unacceptable risk in the investigator´s opinion, may have IP dosing temporarily interrupted until the adverse event returns to ≤ Grade 1 or baseline state. This decision is not dependent on the relationship between the AE and IP (related or not). Recommended dose modifications for *other* ≥ Grade 2 hematologic or non-hematologic adverse events are summarized in Table 4.

Table 4: Guidelines for CC-486 Toxicity Management and Dose Modifications

NCI CTCAE Toxicity Grade	Action
Febrile Neutropenia (≥ Grade 3)	• Continue IP at the discretion of the investigator – If episode persists for ≥ 4 days despite adequate/maximal antibiotic, antiviral and/or antifungal therapy, IP should be temporarily interrupted. – Resume IP at the same dose after the fever has resolved and the ANC has improved or stabilized (as assessed by the investigator). IP should not be resumed for at least 3 days following resolution of fever. Guidance for the use of growth factors and prophylactic antibiotics is provided in Section 9.1. • If a subject experiences febrile neutropenia in 2 consecutive cycles, the steps noted above should be followed, but the IP dose should be reduced by at least 1 step upon resumption of treatment with IP. Secondary prophylaxis with G-CSF may be considered. If subject continues to experience febrile neutropenia episodes that are deemed to be related to IP by the investigator, the dose and schedule may be modified further according to Table 3.
Neutropenia Grade 4 (related or unrelated to IP)	**Pre-existing Neutropenia Grade 4** • Continue IP at the discretion of the investigator – If the neutropenia continues to worsen significantly under treatment in the investigator's opinion, treatment may be temporarily interrupted. – Resume IP after the ANC has improved or stabilized (as assessed by the investigator). IP dose/schedule may be reduced at the investigator´s discretion (see Table 3). • If the subject continues to experience Grade 4 neutropenia during 2 consecutive cycles, IP dose/regimen should be reduced by at least 1 step (Table 3). Secondary prophylaxis with G-CSF may be considered. **Subjects experiencing worsening of Neutropenia to Grade 4 during IP treatment** • Continue IP at the discretion of the investigator – If episode persists for ≥ 4 days, IP may be temporarily interrupted. – Resume IP after the ANC has improved or stabilized (as assessed by the investigator). IP dose/schedule may be reduced at the investigator´s discretion (see Table 3). • If the subject continues to experience Grade 4 neutropenia during 2 consecutive cycles, IP dose/regimen should be reduced by at least 1 step (Table 3). Secondary prophylaxis with G-CSF may be considered.
Diarrhea (≥ Grade 2)	• Interrupt IP and provide adequate/maximum medical intervention • Resume IP at same dose when toxicity resolves to ≤ Grade 1 • If event reoccurs upon re-challenge or during the subsequent treatment cycle, modify IP dose/schedule by at least 1 step according to Table 3.

Table 4: Guidelines for CC-486 Toxicity Management and Dose Modifications (Continued)

NCI CTCAE Toxicity Grade	Action
Nausea and/or Vomiting (≥ Grade 3)	• Interrupt IP and provide adequate/maximal medical intervention • Resume IP at same dose when toxicity resolves to ≤ Grade 1 • If event reoccurs upon re-challenge or during the subsequent treatment cycle, modify IP dose/schedule by at least 1 step according to Table 3.
Renal Dysfunction	• For unexplained elevations of serum creatinine, delay the start of the next cycle of treatment until values return to baseline. Reduce IP dose in the next cycle of treatment by at least 1 step. • The treatment dose and/or schedule can be reduced per Table 3 if the elevation of serum creatinine recurs in the subsequent cycle. • Discontinue IP if similar unexplained renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment.
Other ≥ Grade 2 AEs	• Consider interrupting IP and provide medical intervention as appropriate • Resume IP at same dose when toxicity resolves to ≤ Grade 1 • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, modify IP dose/schedule according to Table 3.

Abbreviations: AE = Adverse Event; ANC = Absolute Neutrophil Count; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte colony-stimulating factor; IP = Investigational Product; NCI = National Cancer Institute.

8.2.4.2. Durvalumab Toxicity Management Guidelines

Dose reduction of durvalumab is not permitted in this study. Guidelines for management of durvalumab-related toxicities are presented in Table 5, Table 6 and Table 7 below.

Table 5: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-Mediated Adverse Events

	Dose Modifications	Toxicity Management
	General Considerations	
	Drug administration modifications of IP/study regimen will be made to manage potential immune-mediated AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of IP/study regimen based on CTC grade/severity (table below), permanently discontinue IP/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of IP/ study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. **Grade 1** - No dose modification **Grade 2** - Hold IP/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • IP/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper • Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with IP/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent. Grade 3 - Depending on the individual toxicity, IP/study regimen may be permanently discontinued. Please refer to guidelines below Grade 4 - Permanently discontinue IP/study regimen	It is recommended that management of immune-mediated adverse events (imAEs) follow the guidelines presented in this table – It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event. – In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start oral prednisone 1-2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – eg, myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2-4 mg/kg/day PO or IV

	• IP Note: IP/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether IP/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper • Note: There are some exceptions to permanent discontinuation of IP for Grade 4 events (ie, hyperthyroidism, hypothyroidism, Type 1 diabetes)	equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg infliximab) – (also refer to individual sections of the immune mediated adverse events for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of IP is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc.). Continuation of IP in this situation should be based upon a benefit/risk analysis for that subject.

AE = adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; imAE = immune-mediated adverse event; IP = investigational product; IV = intravenous; NCI = National Cancer Institute; PO = By mouth; TNF = tumor necrosis factor

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding IP/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold IP/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate IP/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue IP/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the subject. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Subjects should be thoroughly evaluated to rule out any

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold IP/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then IP/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life- threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue IP/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; IP/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue IP/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-mediated hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTs)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold IP/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume IP/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold IP/study regimen dose until resolution to Grade ≤1 or baseline • Resume IP/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue IP/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue IP/study regimen. Permanently discontinue IP/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue IP/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (ie, mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-mediated hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [eg, portal vein thrombosis]). – For HBV+ subjects: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ subjects: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any subject with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold IP/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume IP/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (ie, liver ultrasound), and consider starting immunosuppressives (ie, mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or	• Hold IP/study regimen dose until resolution to Grade ≤1 or baseline • Resume IP/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue IP/study	**For Grade 3:** – Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days Permanently discontinue IP/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue IP/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (eg, fever, elevated INR): - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: Permanently discontinue IP/study regimen**			

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold IP/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume IP/study	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		regimen after completion of steroid taper.	clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume IP/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue IP/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND IP DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled IP/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold IP/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the IP/study regimen does not provide improvement of the Grade 3 skin rash	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		to Grade ≤1 or baseline within 30 days, then permanently discontinue IP/study regimen. **For Grade 4:** Permanently discontinue IP/study regimen.	– Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (eg, blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor subject with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold IP/study regimen dose until subject is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. IP/study regimen can be resumed once event stabilizes and after completion of steroid taper. Subjects with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with IP/study regimen on the following conditions:	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all subjects with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without IP/study regimen interruption, and without corticosteroids.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		1. The event stabilizes and is controlled. 2. The subject is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without IP/study regimen interruption, and without corticosteroids. – Once subjects on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For subjects with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold IP/study regimen dose until endocrinopathy symptom(s) are controlled. IP/study regimen can be resumed once event stabilizes and after completion of steroid taper. Subjects with endocrinopathies who may require prolonged or continued steroid replacement (eg, adrenal insufficiency) can be retreated with IP/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The subject is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all subjects with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (eg, hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without IP/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without IP/study regimen

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		≤10 mg/day or equivalent.	interruption, and without corticosteroids. – Once subjects on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold IP/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding IP/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. IP/study regimen can be resumed	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to

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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
	Grade 2	Hold IP/study regimen dose until resolution to Grade ≤1. Permanently discontinue IP/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat

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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		instability. **For Grade 4:** Permanently discontinue IP/study regimen.	supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in subjects with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor subjects for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			– Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (eg, BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold IP/study regimen dose during diagnostic work-up for other etiologies. If IP/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening	- If Grade 2 -- Hold IP/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate IP/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue IP/study regimen. If Grade 3-4, permanently discontinue IP/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support))		antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor subjects for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold IP/study regimen dose until resolution to Grade ≤1. - Permanently discontinue IP/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold IP/study regimen dose until resolution to Grade ≤1. Permanently discontinue IP/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue IP/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether subject may require IVIG,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			plasmapheresis. – Once the subject is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

AChE = Acetylcholine esterase; ADL = Activities of daily living; AE = Adverse event; ALP = Alkaline phosphatase test; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = Blood urea nitrogen; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; DM = diabetes mellitus; ECG = electrocardiogram; HBcAB = hepatitis B core antibody; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HgA1c = hemoglobin A1c; IG = immunoglobulin; ILD = Interstitial lung disease; imAE = immune-mediated adverse event; INR = international normalized ratio; IP = investigational product; IV = Intravenous; IVIG = intravenous immunoglobulin; GI = Gastrointestinal; LDH = lactic dehydrogenase; LFT = Liver function tests; LLN = Lower limit of normal; MRI = Magnetic resonance imaging; NCI = National Cancer Institute; NCCN = National Comprehensive Cancer Network; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = By mouth; T3 = Triiodothyronine; T4 = Thyroxine; TB = Total bilirubin; TNF = Tumor necrosis factor; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.

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

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

Table 6: Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-Related Reactions

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

Abbreviations:
IM = intramuscular; IP = investigational product; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 7: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-Immune-Mediated Reactions

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

Abbreviations:
AEs = adverse events; IP = investigational product; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

8.2.5. Re-treatment Criteria

In order to proceed to the next cycle, subjects must continue to meet entry criteria regarding renal and hepatic function (see Section 7.3). Thus subjects will have laboratory assessments performed to evaluate organ function prior to starting each cycle (including Cycle 1). Because of the time it takes to obtain results from the central laboratory, samples should be collected early enough prior to starting the next cycle in order to allow sufficient time for review. In the event that immediate laboratory assessment is needed, local laboratory measurement is acceptable for starting the next cycle pending the outcome of the central laboratory assessment (ie, in addition to collecting the local laboratory sample, a matching sample should always be sent to the central laboratory).

The start of the next cycle will be delayed if the subject does not meet entry criteria regarding renal and hepatic function. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the medical monitor must be consulted. Study treatment should be discontinued if there is a delay of more than 56 days (8 weeks) in the start of the next cycle, unless, in the opinion of the investigator and the medical monitor, the subject is experiencing clinical benefit. Justification of the subject continuing in the study must be recorded in the source documents.

Prior to discontinuing a subject, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion. The decision to discontinue a subject remains the responsibility of the treating physician and will not be delayed or refused by the sponsor.

8.2.6. Overdose

Overdose, as defined for this protocol, refers to CC-486 and durvalumab dosing only.

On a per dose basis, an overdose is defined as ***any amount*** over the protocol-specified dose of CC-486 or durvalumab assigned to a given subject, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as any amount more frequent than the protocol-required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

- For oral, any amount over the protocol-specified dose
- For IV, 10% over the protocol-specified dose

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.

8.2.7. Discontinuation

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

- Lack of efficacy
- Progressive disease

- Withdrawal by subject
- Adverse event(s)
- Death
- Loss to follow-up
- Protocol violation
- Study termination by the Sponsor
- Pregnancy
- Recovery
- Non-compliance with IP
- Transition to commercially available treatment
- Physician decision
- Disease relapse
- Symptomatic deterioration
- Protocol violation
- Other (to be specified on the eCRF)

Because a hematologic response to treatment with CC-486 may be delayed, it is recommended that subjects receive at least 6 cycles of treatment with the IP; however, subjects may be discontinued from treatment at the investigator's discretion prior to reaching the recommended minimum number of cycles for any of the reasons detailed above. The reason for discontinuation should be recorded in the CRF and in the source documents.

8.3. Method of Treatment Assignment

Subjects will be enrolled via IRTS to ensure timely registration and to facilitate subject tracking and IP resupply needs.

Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to call into the IRTS to enroll a subject. At screening, the investigator or designated staff will call into the IRTS and provide the requested identifying information for the subject. The IRTS will then confirm the assignment of a unique subject number. Once assigned to a subject, the subject number will not be reused. If a subject is screened but not enrolled, the screen-failure must be registered using the IRTS. During the treatment phase, calls will be placed to the IRTS for each new allocation of IP to a subject, to acknowledge receipt of additional IP shipments to the site, and to register changes in a subject's status (eg, drug hold, dose modification, or treatment discontinuation). Details regarding use of the IRTS are found in the IRTS User Manual.

8.4. Packaging and Labeling

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

No blinding is applied in this study.

8.5. Clinical Supplies

The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying shipping order form. The investigator(s) or designee(s) will verify the accuracy of the information on the form and call the IRTS to register the IP received at the site.

At the study site, all IP will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on the package label at a controlled temperature, and a temperature log must be maintained in the source documents.

8.6. Investigational Product Accountability and Disposal

Investigational product accountability will be assessed by the investigator or designee. Applicable information such as lot number, tablet or vial count, and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary).

Investigational product accountability should be assessed before drug dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the treatment discontinuation visit.

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

A copy of the site's Standard Operating Procedure (SOP) for drug destruction may be collected by the sponsor (or designee). Any revisions to a site's destruction process must be provided and

approved by the sponsor (or designee) prior to implementation of this protocol. Any site without a sponsor (or designee)-approved destruction SOP and process will be required to return IP to Celgene. 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 Celgene (or designee).

8.7. Investigational Product Compliance

Subjects will self-administer CC-486 doses in the treatment phase. Durvalumab will be administered at the study site. Documentation of dosing during treatment will be recorded in a study-specific diary card. Investigational product administration diary cards will be provided by the sponsor to study site personnel, who will in turn distribute them to study subjects. Study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day, and any other applicable information. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Subjects (or legally authorized representative) will be asked to record IP dosing information in the diary card and to bring the diary card and unused tablets in the blister card (or the blister card packaging even if it is empty) with them to scheduled clinic visits (ie, prior to the start of the next treatment cycle). A diary card and tablet compliance check will be performed by study personnel. Diary cards must be saved and kept with the source documentation. Study site personnel will perform an IP administration compliance check and record this information in the subject's source documentation and on the appropriate CRF.

Administration of all IP will be recorded, including dispensing, dosing, and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All prior and concomitant medications (prescription and non-prescription), treatments, and therapies taken from 28 days (4 weeks) prior to the first dose of IP, up to 28 days after the last dose of CC-486 (90 days for durvalumab), or up to the last study visit, whichever date is later, must be recorded on the appropriate CRF.

All prior treatments for MDS, including ESAs, thrombopoiesis-stimulating agents (TSAs), iron-chelating agents, chemotherapy, cytotoxic therapy, investigational agents, or other medications considered supportive care for MDS should be recorded on the respective CRF(s) regardless of discontinuation date of treatment.

Concomitant medications should be kept to a minimum during the study. However, if considered necessary for the subject's welfare and are unlikely to interfere with the IP, they may be given at the discretion of the investigator.

9.1. Permitted Concomitant Medications and Procedures

Best supportive care may be used in combination with study therapy if deemed necessary. Best supportive care for this study includes, but is not limited to, treatment with RBC or whole blood transfusions, fresh frozen plasma transfusions, single donor or pooled donor platelet transfusions, antibiotic, antiviral and/or antifungal therapy, nutritional support as needed, and myeloid growth factors (G-CSF and GM-CSF) for subjects experiencing neutropenic infections. The use of myeloid growth factors is also allowed for secondary prophylaxis under certain conditions as described below. The use of these products will be considered as concomitant treatment and documented as concomitant medications, therapies or procedures.

Blood product support (RBCs and platelets) may be administered according to institutional standards. RBC and platelet transfusions will be considered concomitant procedures and should be collected on the appropriate CRF.

Subjects who are currently using iron-chelating agents should be on a stable or decreasing dose for at least 8 weeks (56 days) prior to enrollment. Initiation, modification, and/or discontinuation of iron-chelating agents during the treatment phase of the study is discouraged and should be discussed with the medical monitor first whenever possible.

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

It is recommended that an antiemetic medication such as a serotonin 5-HT_3 receptor antagonist (eg, ondansetron) be taken 30 minutes prior to IP administration during Cycle 1 of the treatment phase. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed. Pre-treatment or post-treatment with a serotonin 5-HT_3 receptor antagonists, or other locally available and appropriate antiemetic medication, will be considered concomitant treatment and should be recorded on the appropriate CRF.

Treatment with antidiarrheal medications is recommended at the first sign of diarrhea as per the guidelines in Appendix H. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 and/or durvalumab may be appropriate. Pre- and post-treatment with an antidiarrheal must be recorded in the CRF as concomitant medication.

Myeloid growth factors (G-CSF and GM-CSF) may be given per investigator's discretion for the treatment of neutropenic fever/infections as well as for secondary prophylaxis if the subject had a previous event of neutropenic fever/infection or neutropenia Grade 4 during the treatment phase of the study and the safety of the subject is considered jeopardized by subsequent episodes of neutropenic fever/infections or Grade 4 neutropenia.

For subjects who develop an ANC < 0.5 x 10^9/L (or per institutional standards), administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin) or other recognized prophylactic antibiotics may be considered and documented as a concomitant medication on the appropriate CRF. If neutropenic fever/infection occurs, treatment should consist of a broad spectrum antibiotic, and if the investigator deems the use of a myeloid growth factor to be medically important, myeloid growth factors may also be administered. For secondary prophylaxis with myeloid growth factors, the dose modification guidelines detailed in Section 8.2.4 remain applicable. Discontinuation of secondary prophylaxis with myeloid growth factors should be considered by the investigator as clinically appropriate.

Concurrent systemic corticosteroids for medical conditions other than MDS are allowed, provided the subject is on a stable or decreasing dose for ≥ 1 week prior to the first dose of IP. Initiation, modification, and/or discontinuation of corticosteroids during the treatment phase of the study is discouraged and should be discussed with the medical monitor first whenever possible.

9.2. Prohibited Concomitant Medications and Procedures

Best supportive care for this study specifically excludes cancer surgery, immunotherapy, biologic therapy, radiotherapy, anticancer hormonal therapy, and systemic chemotherapy where the goal is to eradicate or slow the progression of the disease.

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

- Cytotoxic, chemotherapeutic, targeted, or investigational agents/therapies
- Azacitidine for injection, decitabine, or other demethylating agents
- Lenalidomide, thalidomide, and other immunomodulatory drugs (IMiDs)
- Erythropoiesis stimulating agents and other hematopoietic growth factors (eg, interleukin-3)
- Romiplostim and other TSAs (eg, Interleukin-11, Eltrombopag)
- Hydroxyurea
- Androgens, unless to treat hypogonadism
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate,

azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (eg, intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, moderate to severe infusion-related reactions, etc.) are acceptable upon discussion and agreement with the medical monitor.

- Live attenuated vaccines during the study through 30 days after the last dose of durvalumab.

Refer to Section 7.3 for exclusion criteria pertaining to prohibited concomitant medications.

9.3. Required Concomitant Medications and Procedures

There are no required concomitant medications, although prophylactic treatment with an antiemetic or antidiarrheal medication may be considered and is recommended during the first cycle of treatment.

10. STATISTICAL ANALYSES

The sections below provide an overview of the proposed statistical considerations and analyses.

10.1. Overview

This is an open-label, randomized 2-arm study to estimate the efficacy of CC-486 as a mono-therapy and CC-486 + durvalumab as a combination therapy in subjects with MDS who fail to achieve an objective response to treatment with azacitidine for injection or decitabine.

The study consists of 5 phases: *Screening, Safety Run-in, Randomized Treatment, Follow-up,* and *Extension*. The randomized treatment phase will be conducted in 2 stages, with a futility assessment planned at the completion of Stage 1 to determine whether the null hypothesis *(H_0: $p < 12.5\%$)* can be rejected with 3 or more responses in Stage 1. If 3 or more responses have been observed before the end of Stage 1, the planned futility assessment may be performed earlier than at the completion of Stage 1 to confirm the finding of responses. This earlier analysis will replace the futility analysis planned at the completion of Stage 1. This earlier futility assessment will have the same integrity as the futility assessment planned at the completion of Stage 1. An analysis will be performed at the completion of Stage 2 to estimate the overall response rate of treatment of all the subjects in the cohort.

The primary objective is to evaluate the treatment response with CC-486 monotherapy and combination therapy in this sample of subjects. The secondary objectives include the evaluation of overall survival, time to response, duration of responses, time to disease progression, and safety and tolerability of the regimen in this population.

This section defines the subject populations for various statistical data analyses, the justifications of sample sizes for the cohorts, and the methodologies that will be used for the efficacy and safety analyses. All statistical analyses specified in this protocol will be conducted using SAS® Version 9.2 or higher unless otherwise specified.

10.2. Study Population Definitions

10.2.1. Intent-to-Treat Population

The intent-to-treat population will include all enrolled subjects who received at least one dose of IP.

10.2.2. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all ITT subjects who have at least one post-baseline efficacy assessment performed, met all inclusion/exclusion criteria, and received a minimum of one cycle of treatment.

10.2.3. Safety Population

The safety population will include all enrolled subjects who have received at least 1 dose of IP and had at least 1 post-dose safety assessment.

10.2.4. Evaluable Population

Intent-to-treat subjects who have at least 1 post-baseline efficacy assessment performed, experienced no major protocol deviations during the study, and have received a minimum of 1 cycle of treatment are considered to be in the evaluable population. This definition will be further clarified in the final statistical analysis plan before database lock.

10.2.5. Pharmacokinetic Population

The pharmacokinetic population will include enrolled subjects who have evaluable concentration data to determine the pharmacokinetic parameters from at least one dose of IP.

10.3. Sample Size and Power Considerations

The sample size required will be identical for each treatment arm in each cohort and is estimated using the optimal design of the Simon's two-stage design method (Simon, 1989). The null hypothesis of the response rate will be tested against a one-sided alternative.

For each cohort, the null hypothesis of the response rate (H0: $p \leq 0.125$) will be tested against the alternative hypothesis of the response rate (H1: $p \geq 0.27$) with a type I error rate of 10% and 80% power. During the first stage, 16 subjects will be accrued per cohort. If there are 2 or fewer responses in these 16 subjects, the cohort will be stopped and no further recruitment will be needed. Otherwise, 25 additional subjects will be accrued per cohort for a total of 41 subjects in each cohort. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected.

For each cohort, in addition to the evaluation of treatment responses based on objective response criteria, the quality of responses will also be considered for the decision whether to continue the cohort to the second stage of the study. *Quality of response* will be assessed based on the magnitude of hematologic and biologic responses observed in individual subjects, with special consideration for response duration and will be specified with more details in the final Statistical Analysis Plan (SAP).

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 percentage 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

All efficacy analyses will be performed on the ITT population.

Supportive efficacy analyses will also be performed using the evaluable population.

10.6.1. Primary Efficacy Analysis

The primary assessment of efficacy will be the overall rate of response (defined as CR, PR, or mCR), and HI as determined using the modified IWG 2006 response criteria for MDS (Appendix F). For hematologic response, CR, PR, and mCR will be determined by investigator assessment (with confirmation by central reviewer), while HI will be derived. The percentage of subjects with the other response outcomes of stable disease, failure, relapse after CR or PR, and disease progression will also be presented. Percentages will also be presented separately for CR, PR, mCR, and HI.

The percent of responders will be estimated using 95% confidence intervals for proportions.

Hematologic response (Complete Remission [CR], Partial Remission [PR], Marrow CR [mCR], Stable Disease [SD], Failure, Relapse after CR or PR, and Cytogenetic Response) is defined according to modified IWG 2006 criteria (Appendix F). Subjects will be classified according to their best response achieved during treatment for the response categories of CR, PR, mCR, SD, and failure. Only subjects who achieve CR or PR will be included in the Relapse after CR or PR category. Subjects will be evaluated for cytogenetic response regardless of their response status in other categories. For cytogenetic response, subjects will be classified as having a complete or partial response based on the best response achieved during treatment. Hematologic response will be presented descriptively using counts and percentages.

The response rates at the end of Stage 2 and the associated 95% confidence interval will be estimated for each cohort which completes Stage 2. Similar estimates for Stage 1 will be provided for any cohort which does not continue to Stage 2. The response rates at the end of Stage 2 will be compared between cohorts of SD and PD subjects (if both cohorts finished Stage 2) using the relative risk ratio or other appropriate methods. Specifically, if relative risk method is used, the ratio of response rates for both cohorts and the associated 95% confidence interval will be estimated.

10.6.2. Secondary Efficacy Analyses

10.6.2.1. Overall Survival

Overall survival (OS), time to death from any cause, will be calculated using date of first dose and date of death, or date of last follow-up for censored subjects. Time to death from any cause is defined as the time between first dose and death from any cause. All subjects will be followed until drop-out, death, or study termination. Drop-out may be due to withdrawal of consent from further data collection or loss to follow-up. Subjects who drop-out or are alive at study termination will have their OS times censored at the time of last contact, as appropriate. The OS curve will be estimated using Kaplan-Meier (KM) method.

10.6.2.2. Time to Onset of Response

Time to onset of first response is defined as the time between the date of first IP dose and the earliest date any response (CR, PR, mCR, or HI) is first observed. Subjects who do not achieve any defined response during the treatment period will be censored at the date of treatment discontinuation, disease progression, or death, whichever occurs first. Time to onset of best

response will be defined in a similar manner. Time to onset of first response and best response for the treatment group will be estimated using KM method.

10.6.2.3. Duration of Response

Duration of hematologic response/improvement will be determined only for subjects who achieve a response on treatment. Duration of hematologic response/improvement is defined as the time from the date response/improvement is first observed until the date the subject has a subsequently documented relapse or disease progression as defined by the modified IWG 2006 criteria. Subjects who maintain hematologic response/improvement through the end of the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Duration of response will be assessed for both first response and best response. Duration of hematologic response/improvement for the treatment group will be estimated using KM method.

10.6.2.4. Progression-free Survival

Progression-free survival (PFS), time to disease progression or death from any cause, will be calculated using date of first dose of IP and the earliest of date of disease progression or date of death, or date of last follow-up for censored subjects. Time to disease progression or death from any cause is defined as the time between first dose and the earliest of disease progression or death from any cause. All subjects will be followed until drop-out, death, or study termination. Drop-out may be due to withdrawal of consent from further data collection or loss to follow-up. Subjects who drop-out or are alive without disease progression at study termination will have their PFS times censored at the time of last contact, as appropriate. The PFS curve will be estimated using Kaplan-Meier (KM) method.

10.6.2.5. Stable Disease

- A subject will be considered as having a stable disease if the disease neither responded nor progressed during or after the treatment.
- The duration of stable disease will be defined as the time between any two observations of objective disease progression (modified IWG criteria – Appendix F), starting from the first day of dosing with IP. Note, objective disease progression requires two observations demonstrating progressive disease, at least 8 weeks apart. The date of disease progression will be that of the earliest observation that is not followed by a discordant observation within the subsequent 8 weeks.
- Subjects who maintain stable disease through the end of the treatment period will be censored at the date of study termination.
- Duration of stable disease will be estimated using KM method.

10.6.2.6. Disease Progression to AML

- Time to AML progression is defined as the time from the date of first dose of IP until the date the subject has documented progression to AML.
- Subjects who do not progress to AML will be censored at the date of last follow-up, the date of death, or the date of study termination.

- Time to AML progression will be estimated using KM method.

10.7. Safety Analysis

The safety population will be used for all safety evaluations.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred term. Adverse events will be summarized by worst severity grade. Adverse events, as well as treatment-emergent AEs, will be summarized by system organ class, and preferred term. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE (Version 4.03) Grade 3 or Grade 4, adverse events related to IP, serious adverse events and Adverse Events of Special Interest (AESI) will be summarized separately.

Clinical laboratory results will be summarized descriptively and will include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and non-hematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized.

Vital sign measurements will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized.

10.8. Interim Analysis

An Independent Data Monitoring Committee will review the safety data during the safety run-in phase. The committee will also review the efficacy and safety data during the randomized phase of the study, in addition to the recommendation for any cohort to continue to Stage 2 of the study. The details of the data monitoring plan will be provided in a separate charter document.

10.9. Additional Analyses

CCI [redacted]

10.9.2. CC-486 PK Analysis

10.9.2.1. 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 quantification (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 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, (Pharsight®, a Certara™ company, St. Louis, Missouri). 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 (MS MIAMI, Miami, Florida).

10.9.2.2. 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 $\geq$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)/ λ_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)/λ_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.

10.9.2.3. Pharmacokinetic Methods

By-subject listing of pharmacokinetic parameters will be provided. The values of 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 (ie, scatter plots, box plots, etc) may be used to visualize the results.

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

CCI [redacted]

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.6 for the definition of overdose.) Any sequelae of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequelae of an overdose is an SAE, then the sequelae must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-486 or durvalumab overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of CC-486, 90 days after the last dose of durvalumab, or until the Treatment Discontinuation Visit, whichever is later 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.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

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

- Results in death;

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

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

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

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

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

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 4.03).

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

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

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

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

11.2.3. Causality

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

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

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

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by 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, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

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

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

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

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

11.4. Pregnancy

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

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 90 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

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

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

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

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

11.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant while the male subject is on IP, or within 90 days of the male subject's 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. Where applicable, the IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the investigator and medical monitor.

11.5. Reporting of Serious Adverse Events

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

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study from the time the subject signs informed consent until 28 days after the last dose of CC-486, 90 days after the last dose of durvalumab, or until the Treatment Discontinuation Visit, whichever is later, and any SAE made known to the investigator at any time thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be collected.

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/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 Institutional Review Board (IRB)/Ethics Committee (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's 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, 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, durvalumab, based on the Durvalumab Investigator's Brochure for the product.

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 (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

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

Celgene Drug Safety Contact Information:

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

11.7. Adverse Events of Special Interest

An adverse event of special interest is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of

AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of these IPs.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions in regards to an adverse event (AE) being an imAE, the investigator should promptly contact the Medical Monitor.

Further information on these AESIs (eg presenting symptoms) can be found in the current version of the Durvalumab Investigator's Brochure (section 5.4.2 Summary of Risks).

11.7.1. Progression to AML

Progression to AML will be monitored as an event of special interest and must be reported as an SAE regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICD until death, loss to follow-up, withdrawal of consent for further data collection, or study closure.

12. DISCONTINUATIONS

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

- Lack of Efficacy
- Progressive Disease
- Withdrawal by Subject
- Adverse Event
- Death
- Loss to Follow-up
- Protocol Violation
- Study Terminated by Sponsor
- Pregnancy
- Recovery
- Non-compliance with IP
- Transition to commercially available treatment
- Physician decision
- Disease relapse
- Symptomatic deterioration
- Protocol violation
- Other (to be specified on the eCRF)

Definitions for progressive disease to be applied under different circumstances (eg, following a RBC-transfusion-independent response to treatment) are provided in Table 8, below. Although lack of efficacy or progressive disease is considered a sufficient reason for discontinuing a subject from IP, the investigator should continue to treat the subject until the investigator considers IP to be no longer beneficial to the subject, or the change of disease state renders the subject unacceptable for further treatment in the judgment of the investigator. Because a hematologic response to treatment with CC-486 may be delayed, it is recommended that subjects receive at least 6 cycles of treatment with the IP; however, subjects may be discontinued from treatment at the investigator's discretion prior to reaching the recommended minimum number of cycles for any of the reasons detailed above.

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, it is recommended that the investigator contact the medical monitor and forward appropriate supporting documents for review and discussion.

The reason for discontinuation should be recorded in the CRF and in the source document for all enrolled subjects, regardless of whether they are dosed or not.

All subjects discontinued from protocol-prescribed therapy for any reason should undergo treatment discontinuation procedures (Section 6.13), and will be followed for a period of at least 28 days following the last dose of CC-486 (90 days after last dose of durvalumab) or until the date of the last study visit, whichever period is longer, as described in Section 6.14.

All subjects discontinued from protocol-prescribed therapy for any reason will also be followed for survival, subsequent MDS therapies, and progression to AML as described in Section 6.14.

Table 8: Definitions of Progressive Disease for Clinical Decisions on Discontinuing Subjects From the Investigational Product and/or From the Study

Category	Progression/Relapse Criteria
Progression in Bone Marrow	For subjects with: • Less than 5% blasts at baseline: ≥ 100% increase to ≥ 8% blasts • ≥ 5% blasts at baseline: ≥ 50% increase to ≥ 10% blasts Note: A 2nd bone marrow sample should be collected within 4 weeks to confirm progression before discontinuing subjects from treatment.
Progression in RBC Transfusion Requirement [a]	For subjects not RBC-transfusion-dependent at baseline: Development of RBC transfusion dependence: ≥ 2 RBC transfusions in any 56-day (8-week) period during study treatment. For subjects RBC transfusion-dependent at baseline who do not achieve RBC transfusion independence ≥ 56 days (8 weeks) during study treatment: > 50% increase in the average RBC transfusion requirement during any 56-day (8-week) period during study treatment compared to the average RBC transfusion requirement in the 56 days (8 weeks) prior to enrollment.
Relapse in RBC Transfusion Requirement [a]	For subjects RBC transfusion-dependent at baseline who do achieve RBC transfusion independence ≥ 56 days (8 weeks) during study treatment: Relapse is defined as a return to baseline RBC transfusion requirement or worse.
Progression in Platelet Transfusion Requirement	For subjects not platelet transfusion-dependent at baseline: Development of platelet transfusion dependence: ≥ 2 platelet transfusions in any 56-day (8-week) period during study treatment. For subjects platelet transfusion-dependent at baseline who do not achieve platelet transfusion independence ≥ 56 days (8 weeks) during study treatment: > 50 % increase in platelet transfusion requirement during any 56-day (8-week) period during study treatment compared to the 56-day (8-week) period prior to enrollment.
Relapse in Platelet Transfusion Requirement	For subjects platelet transfusion-dependent at baseline who achieve platelet transfusion independence ≥ 56 days (8 weeks) during study treatment: Relapse is defined as a return to baseline requirement or worse.

Abbreviations: MDS = myelodysplastic syndrome; RBC = red blood cell.

[a] RBC transfusions administered for surgical procedures, significant hemorrhagic events, or other reasons documented as unrelated to MDS-associated anemia will not be counted in the assessment of baseline RBC transfusion requirements, efficacy, or progressive disease status.

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

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

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by GCP, as described in International Council for 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. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

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

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

14.3. Subject Information and Informed Consent

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

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICD 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 ICD 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 ICD. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4. Confidentiality

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

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

14.5. Protocol Amendments

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

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

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

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 informed consent document 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. Closure of the Study

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

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

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

The sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In the case where there are subjects in the Extension Phase continuing to receive investigational product who, in the opinion of the investigator(s) would continue to receive benefit from treatment, the sponsor may choose to initiate an open-label rollover study under a separate protocol to allow these subjects to continue receiving oral azacitidine.

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 SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

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

- Signed 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 standard operating procedures.

16.1. Study Monitoring and Source Data Verification

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

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consent documents, 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/ECs, regulatory authorities (eg, United States Food and Drug Association [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16.3. Product Quality Complaint

A Product Quality Compliant (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient.

Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing PPD or by contacting the Celgene Customer Care Center PPD

17. PUBLICATIONS

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

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19. APPENDICES

Appendix A: Myelodysplastic Syndromes World Health Organization Classification System

Myelodysplastic Syndromes World Health Organization Classification System		
	Definition	
Category	Peripheral Blood Smear Evaluation	Bone Marrow Evaluation
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (< 1%)[b]	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ringed sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with Multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[b] No Auer rods < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ±15% ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts[b] No Auer rods < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[b] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts[•] Auer rods[c] < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[c] Auer rods[c]
Myelodysplastic syndrome - unclassified (MDS-U)	Cytopenias < 1% blasts[b]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS[•]
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.
[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have 5%

blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rods + and/or 5% to 19% blasts in the blood.

[d] Includes unbalanced abnormalities -7 or del(7q), -5 or del(5q), i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), balanced abnormalities t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.1), T2;11)(p21;q23), inv(3)(q21q26.2), and t(6;9)(p23;q34), and complex karyotype (3 or more chromosomal abnormalities) involving one of more of the listed abnormalities.

Sources: Brunning RD, Bennett JM, Flandrin G, Matutes E, Head D, Vardiman JW, et al. Pathology and genetics of tumors of hematopoietic and lymphoid tissues. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classification of tumors. Lyon (France): IARC Press; 2001. p. 63-73.

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Appendix B: French-American-British (FAB) Myelodysplastic Syndrome (MDS) Classification System

MDS Subtype	Peripheral Blasts (%)	Bone Marrow Blasts (%)	AML Transformation	Median Survival (months)	MDS Diagnoses (%)
Refractory anemia (RA)	**≤1**	**<5**	**10-20**	**30-65**	**10-40**
Refractory anemia with ringed sideroblasts (RARS)	**≤1**	**<5**	**10-35**	**34-83**	**10-35**
Refractory anemia with excess blasts (RAEB)	**<5**	**5-20**	**>50**	**8-18**	**25-30**
Refractory anemia with excess blasts in transformation (RAEB-T)	**≥5**	**21-29**	**60-100**	**4-11**	**10-30**
Chronic myelomonocytic leukemia (CMML)	**<5**	**≤20**	**>40**	**15-32**	**10-20**

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.
Data from Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; 51:189–199.

Appendix C: International Prognostic Scoring System Score

International Prognostic Scoring System for MDS					
	Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone Marrow Blasts (%)	< 5	5-10	-	11-20	21-30
Karyotype[a]	Good	Intermediate	Poor	-	-
Cytopenias[b]	0 or 1	2 or 3	-	-	-

[a] Good: normal, -Y, del(5q), del(20q); Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate: other abnormalities.

[b] Defined as: Hemoglobin < 100 g/L, absolute neutrophil count < 1.8 x 10^9/L, and platelet count < 100 x 10^9/L.

Note: Scores for risk groups are as follows: Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5-2.0; and High: ≥ 2.5.

Source: Greenberg, P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89:2079-88.

Appendix D: International Prognostic Scoring System Score - Revised

IPSS-R Cytogenetic risk groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Intermediate	Poor	Very Poor
Bone Marrow Blast (%)	≤2	-	>2 - <5	-	5 - 10	>10	-
Hemoglobin (g/dL)	≥10	-	8 - <10	<8	-	-	-
Platelets (x10^9/L)	≥100	50 - <100	<50	-	-	-	-
ANC (x10^9/L)	≥0.8	<0.8	-	-	-	-	-

IPSS-R Prognostic Risk Categories/Scores*

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	No. pts	Very Low	Low	Intermediate	High	Very High
Patients (%)	7012	19%	38%	20%	13%	10%
Survival***	-	8.8	5.3	3.0	1.6	0.8
AML/25%***,^	-	NR	10.8	3.2	1.4	0.7

*Greenberg, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndrome. Blood. 2012;120(12):2454-65.

**Schanz J, Tüchler H, Solé F, Mallo M, Luño E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30(8):820-9.

***Medians, years.

^Median time to 25% AML evolution.

Appendix E: Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 1982; 5(6):649-55.

Appendix F: Hematologic Response and Improvement According to the International Working Group for MDS – modified

Hematologic Response Modified from IWG Criteria for MDS (Cheson, 2006)	
Category	**Response Criteria (responses must last at least 4 weeks)**
Complete Remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines• Persistent dysplasia will be noted[a,]• Peripheral blood• Hgb ≥ 11 g/dL Platelets ≥ 100 X 10^9/L Neutrophils ≥ 1.0 X 10^9/L[b] Blasts 0%
Partial Remission (PR)	All CR criteria if abnormal before treatment except: – Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% – Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable Disease (SD)	Failure to achieve any objective response (CR, PR, mCR, or HI), but no evidence of disease progression over any 8-week period
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pre-treatment[d].
Relapse After CR or PR	At least 1 of the following demonstrated by ≥ 2 values, separated by ≥ 2 weeks: – Return to pre-treatment bone marrow blast percentage – Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets – Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete: – Disappearance of the chromosomal abnormality without appearance of new ones Partial: – At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: – Less than 5% blasts: ≥ 100% increase in blasts to ≥ 8% blasts – ≥5% blasts: ≥ 50% increase to ≥ 10% blasts[d] Any clinical worsening from pre-injectable HMA baseline condition, including: – sustained clinically-significant worsening (investigator's assessment) from baseline granulocyte, platelet, or hemoglobin values (≥ 2 values, separated by ≥ 2 weeks) o worsening granulocytes should be ≥ 50% decrease from pre-injectable HMA baseline value o worsening platelets should be ≥ 50% decrease from pre-injectable HMA baseline value o worsening hemoglobin should be ≥ 1.5 g/dL decrease from pre-injectable HMA baseline value – ongoing or worsening RBC or platelet transfusion requirement

Hematologic Response Modified from IWG Criteria for MDS (Cheson, 2006)	
Category	**Response Criteria (responses must last at least 4 weeks)**
Survival	Endpoints: – Overall: death from any cause – Event free: failure or death from any cause – PFS: disease progression or death from any cause – DFS: time to relapse – Cause-specific death: death related to MDS

CR = complete remission; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; HMA = hypomethylating agentl; IWG = International Working Group; mCR = marrow complete remission; MDS = myelodysplastic syndromes; PFS = progression-free survival; PR = partial remission; RBC = red blood cell; SD = stable disease; wks = weeks.

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG (2000) response criteria.

[c] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

[d] 20 – 30% blasts is considered AML according to the WHO classification (Vardiman, 2009).

Notes: Deletions to the IWG response criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006; 108(2): 419-25.

Hematologic Improvement According to IWG Criteria (Cheson, 2006)	
Hematologic improvement[a]	**Response criteria (responses must last at least 8 week)[b]**
Erythroid Response (HI-E) (pre-treatment, < 11 g/dL)	– Hemoglobin increase by ≥ 1.5 g/dL – Relevant reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk
Platelet Response (HI-P) (pre-treatment, < 100 X 10^9/L)	– Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets – Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%[b]
Neutrophil Response (HI-N) (pre-treatment, < 1.0 X 10^9/L)	– At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HI[c]	At least 1 of the following: – At least 50% decrease from maximum response levels in granulocytes or platelets – Reduction in Hgb by ≥ 1.5 g/dL – Transfusion dependence

KEY: HI-E = hematologic improvement-erythroid response; HI-N = hematologic improvement-neutrophil response; HI-P = hematologic improvement-platelet response; IWG = International Working Group; RBC = red blood cell.

[a] Pre-treatment counts averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).

[b] Modification to IWG (2000) response criteria.

[c] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Note: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006; 108(2): 419-25.

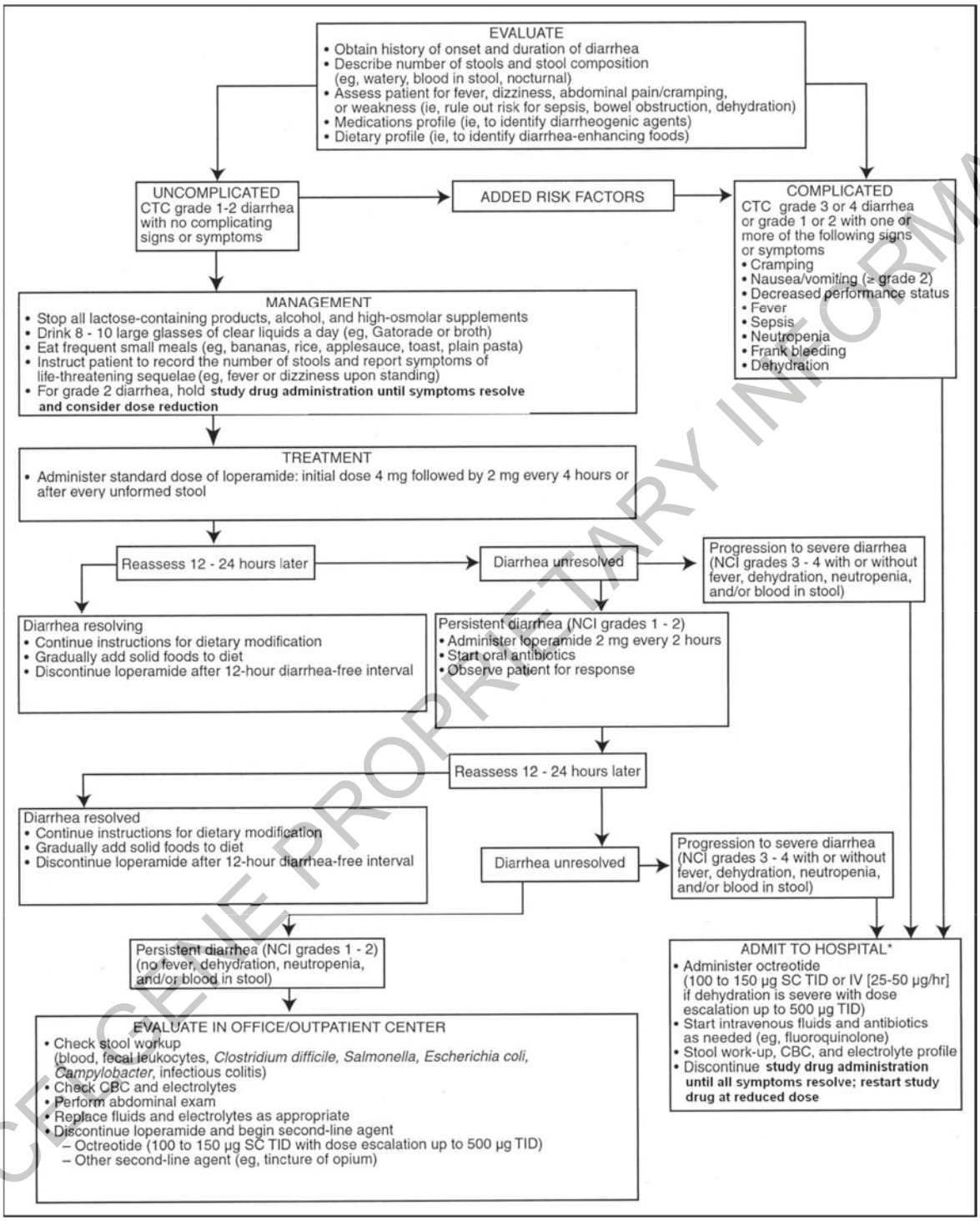
Appendix G: New York Heart Association Classification for Congestive Heart Failure

Functional Capacity
Class I. Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: AHA Medical/Scientific Statement: 1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients With Diseases of the Heart. Circulation. 1994;90:644-645.
Available from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

Appendix H: Recommendations for Management of Treatment-Induced Diarrhea

Published guidelines (Benson, 2004) were modified to be consistent with the clinical protocol.



Key: CBC = complete blood count; CTC = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; SC = subcutaneous; TID = three times daily.

Appendix I: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransaminase (also SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Accumulation ratio
AST	Aspartate aminotransaminase (also SGOT)
AUC	Area under the concentration-time curve
AZA	Azacitidine
BID	Twice daily
BLQ	Below the limit of quantification
BM	Bone marrow
BUN	Blood urea nitrogen
C1D1	Cycle 1, Day 1
CBC	Complete blood count
CCR	Conventional care regimen
CD	Cluster of differentiation
CL	Clearance
Cmax	Maximum observed concentration
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete remission
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off

Abbreviation	Definition
DCR-24w	Disease control rate at 24 weeks
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
EU	European Union
FAB	French-American-British
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
Fe/TIBC	Serum iron/serum total iron-binding capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GDMS	Global de-methylation score
GGT	Gamma glutamyltransferase
GM-CSF	Granulocyte macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HgB	Hemoglobin
HI	Hematologic improvement
HI-E	Hematologic improvement-erythroid response
HI-N	Hematologic improvement-neutrophil response
HI-P	Hematologic improvement-platelet response
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMA	Hypomethylating agent

Abbreviation	Definition
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
iHMA	Injectable hypomethylating agent
imAE	Immune-mediated adverse event
IMiD	Immunomodulatory drug
INR	International Normalized Ratio
INT-1	Intermediate-1
INT-2	Intermediate-2
IP	Investigational Product
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System - Revised
IRB	Institutional Review Board
IRTS	Interactive Response Technology System
ITT	Intent-to-treat
IV	Intravenous
IWG	International Working Group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MAD	Maximum administered dose
mCR	Marrow complete remission
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MDS-U	Myelodysplastic syndrome – unclassified
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
CCI	[redacted]
miRNA	microRNA
MTD	Maximum tolerated dose
NAb	Neutralizing ADA
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviation	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Overall rate of objective response
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PQC	Product Quality Complaint
PR	Partial response
pRBC	Packed red blood cells
PT	Prothrombin time
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QD	Once daily
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ringed sideroblasts
RBC	Red blood cell
RCMD	Refractory cytopenia with multilineage dysplasia
RCUD	Refractory cytopenia with unilineage dysplasia
RDW	Red cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
RN	Refractory neutropenia
RNA	Ribonucleic acid
RT	Refractory thrombocytopenia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation	Definition
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase (also AST)
SGPT	Serum glutamic pyruvate transaminase (also ALT)
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TIL	Tumor-infiltrating lymphocyte
TNBC	Triple-negative breast cancer
TNF	Tumor-necrosis factor
TNM	Tumor, nodes, metastasis
TSA	Thrombopoiesis-stimulating agent
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USA	United States of America
WBC	White blood cell
WHO	World Health Organization
WT	Weight

Appendix J: Extension Phase

Upon Protocol Amendment 4 approval at the respective sites, eligible subjects can enter the Extension Phase.

Subject Eligibility

At the Investigator's discretion and following confirmation of eligibility criteria below, subjects can enter the Extension Phase:

- Subjects who have signed the informed consent for the EP of the study;
- Subjects receiving oral azacitidine and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral azacitidine in the EP;
- Subjects who do not meet any of the criteria for study discontinuation (see Section 12).

Treatment Assignment

Upon approval of Amendment 4, subjects will start the EP at the start of their next regularly scheduled dosing cycle for oral azacitidine and align the Cycle ***X*** Day 1 visit with the Treatment Discontinuation Visit (***X***= most recent cycle during the treatment phase), so they occur on the same day. The dose and schedule will follow the study treatment administration and schedule (Section 8.2). Subjects will remain at the same dose levels from the main study during the Extension Phase and may decrease dose levels following dose modifications (Section 8.2.4); however, dose levels will not increase. Any potential dose escalation will be considered a treatment failure and the subject will be discontinued.

Cycles should be repeated every 28 days. Subjects should be monitored locally for hematology and chemistry testing, pregnancy testing for FCBP and dose-limiting toxicities before the dosing of the next cycle. Dosage delay or reduction as described below may be necessary.

Management of Toxicities and Dose Modifications

Subjects should be monitored for toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03), as a guide for the grading of severity. If a certain level of toxicity is observed and considered by the Investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. In all cases, the reason for dose modification must be recorded in the subject's medical record and corresponding eCRF page. If the subject discontinues the protocol-prescribed therapy because of an AE, this event must be reported in accordance with the procedures outlined in Section 12.

Oral azacitidine dose modifications due to nonhematological and hematological toxicities during oral azacitidine treatment should be managed as described in Section 8.2.4 for dose modification guidelines due to toxicity.

Any potential dose escalation will be considered a treatment failure and the subject will be discontinued.

Adverse Events

Adverse events (non-serious and serious) will continue to be collected in the CRF.

For subjects entering the EP, ongoing AEs at the time of the Treatment Discontinuation Visit (in the main study) should be left as ongoing and should not be recorded again in the EP AE CRF. Adverse events with an onset date equal to or after the EP informed consent date should be recorded in the EP AE CRF. If a previously reported AE worsens during the EP, then the AE should be recorded as a new AE with a higher grade on the EP AE CRF. All subjects will be monitored for AEs for 28 days following the date of last dose of IP. Any SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (return to baseline), recovered with sequelae, or death (due to the SAE). Refer to Section 11 Adverse Events for reporting requirements, responsibilities and procedures.

Concomitant Medications

All concomitant medications that are necessary for the subject's welfare may be given at the Investigator's discretion during the EP and recorded in the CRF. However, treatment with any other investigational medication is not permitted. Refer to Section 9 for prohibited concomitant medications/therapy for subjects on oral azacitidine.

Survival Follow-up

No Survival Follow-up will be required for any subjects in the EP.

Monitoring of Subjects

The monitoring of subjects is to be conducted as per the local standard of care, and include at least:

- Complete blood count with WBC differential and platelet count as required, and at a minimum, prior to each dosing cycle
- For FCBP, pregnancy testing must be done and have a negative result prior to initiating a new cycle
- Bone marrow biopsy and aspirate as clinically indicated
- Additional tests or more frequent monitoring are at the Investigator's discretion based on the subject's clinical status.

Investigator's Responsibility

- Obtain subject's signature of the informed consent form to enter the EP phase
- Monitoring of subjects (listed above)
- Complete Extension Phase case report form pages
- Document all adverse events (serious and non-serious) on the adverse event log page of the Extension Phase CRF as required by the protocol (Section 8.2.4)
- Report serious adverse events and other immediately reportable events, as required by the protocol (see Section 11). A completed SAE form must be faxed to Celgene Drug Safety, as detailed in the Serious Adverse Event Report Form Completion Guidelines, immediately (ie, within 24 hours of the Investigator's knowledge of the event)
- Dispensing and accountability of drug including patient drug diary cards

- Report to the sponsor and complete the CRF for Extension Phase termination when the subject terminates treatment with oral azacitidine.
- The subject should stop treatment with oral azacitidine if any of the following occur:
  - Additional investigational treatment is started;
  - Subject is no longer receiving clinical benefit, as per the Investigator's discretion;
  - Subject has any AE which would result in treatment discontinuation as per the Investigator's discretion
  - Subject withdraws consent;
  - A positive pregnancy test in a FCBP, at any time; or
  - At the specific request of the sponsor or its authorized representative.
- The Investigator must be available for periodic monitoring visits and allow the sponsor access to all medical records.
- The Investigator will maintain source documents for subjects entering the EP for all case report form data points, which include the following:
  - Informed consent;
  - Adverse events (including serious adverse events);
  - Dosing information (date of administration, dose, number of tablets used, and lot number);
  - Concomitant medications; and
  - Termination date and reason.

Statistical Methods

Safety evaluation for the EP will include monitoring for adverse events and recording of concomitant medications. Although physical examinations, vital sign measurements and laboratory assessments will be performed in the EP, these assessments will not be captured in the CRF. However, clinically significant findings from these assessments which meet the definition of an adverse event (see Section 11) will be reported as adverse events. Adverse events will be summarized as per Section 10.7 on the subjects entering the EP. Exposure to oral azacitidine as well as concomitant medications taken during the EP will also be summarized.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: PPD
Title: PPD
Date: Friday, 21 June 2019, 02:28 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Based on Protocol Section 4.1.7 (Study Closure), the timing for the primary analysis and potential closure of the study will be met shortly. Also in line with this section, Celgene is adding an Extension Phase for all currently active subjects who are receiving treatment and opt to continue with CC-486.

Study enrollment was closed on 29 Jun 2018. Enrollment in the Phase 1 safety run-in portion for CC-486 Monotherapy was completed with 13 subjects in the Phase 1 CC-486 Monotherapy cohort on 07 Sep 2017. The Phase 1 Combination Therapy Cohort was stopped on 16 Jan 2018 due to challenges in finding the optimal combination dose. The Phase 2 Monotherapy SD and PD cohorts fully enrolled for Stage 1 in December 2017 and June 2018, respectively. However, the minimal number of responses required to proceed to Stage 2 was not met and the Phase 2 cohorts were closed on 29 Jun 2018. Six subjects are ongoing in the Monotherapy SD/PD cohorts.

Per protocol, the primary analysis will be conducted once all subjects enrolled have completed 12 months of treatment or have discontinued before reaching 12 months of treatment, whichever occurs first.

Significant changes included in this amendment are summarized below:

- A description of the Extension Phase is presented in Appendix J and mentioned throughout the protocol. The overall duration of the study will be extended during the Extension Phase.
  - Revised sections: Protocol Summary, Sections 4.1.6 Extension Phase, and 6.15 Extension Phase, Figure 1, Table 2 (Table of Events) and Appendix J: Extension Phase; and other editorial changes in the protocol for the extension phase.

The amendment also includes other minor clarifications and corrections:

- Protocol Summary and Section 4.1: Information was updated on enrollment closure, the Extension Phase, and the number of subjects who are ongoing.
- Section 4.1.7, 4.4, and 14.8: Language was added on the timing of study closure.
- Section 4.3: Total study duration was updated to include the Extension Phase.
- Section 8.1.1: The available CC-486 supply was modified due to current subjects only taking 100 mg tablets. "After Amendment 4 approval, the CC-486 supply will be limited to 100-mg tablets for oral administration."
- Section 8.2.4: Restrictions were added to dose increase modifications during the Extension Phase.
- Section 11.6: The following text was deleted: "Adverse events such as death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities. These events will be captured as AEs on the CRF, reported to Celgene Drug Safety meeting SAE reporting criteria (within 24 hours) and reported to regulatory authorities in the annual report."

The amendment also includes several other minor clarifications and typographical corrections.

1. JUSTIFICATION FOR AMENDMENT

This protocol was amended as follows:

- Protocol text was updated to allow the dose escalation of CC-486 after 2 well-tolerated cycles (instead of 4 cycles). The safety assessment observed in the Phase 1 safety run-in portion of the trial was based on 2 dosing cycles and most adverse events occurred early in these cycles. Thus, it is reasonable that in the absence of unacceptable toxicity, subjects who show signs of worsening disease (clinical or hematological), who remain in stable disease, or do not experience modified International Working Group (IWG) 2006 hematologic improvement (HI) or better (partial response [PR], complete response [CR] or marrow CR – modified IWG 2006) can dose escalate after 2 well-tolerated cycles.

  We have also added the text "who remain in stable disease" for clarity that stable disease patients may also dose escalate after 2-well tolerated cycles.

  Revised sections include Section 4.1.3 Randomized Treatment Phase, Section 6.5 CC-486 (Oral Azacitidine), Section 8.2 Treatment Administration and Schedule, and Section 8.2.4.1 CC-486 (Oral Azacitidine) Dose Modification and Toxicity Management.

- The dosing modification and Toxicity Management Guidelines have been updated for consistency with recommendations in the most recent Durvalumab Investigator's Brochure Edition 12.

  Revised sections: Table 5: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-Mediated Adverse Events, Table 6: Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-Related Reactions, and Table 7: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-Immune-Mediated Reactions.

- To be consistent with the Durvalumab Investigator's Brochure Edition 12, the term "immune-related adverse event (abbreviated as irAE) has been changed to "immune-mediated adverse event" (abbreviated as imAE) throughout the protocol text.

  Sections revised include Protocol Summary, Section 4.1.2.2 Durvalumab / CC-486 Combination Therapy Dose-Limiting Toxicity, Section 4.1.3 Randomized Treatment Phase, Section 6.7 Safety, Table 5 Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-Mediated Adverse Events, Section 11.7 Adverse Events of Special Interest, Appendix I List of Abbreviations and Definitions of Terms.

- CCI [redacted]

CCI [redacted]

- Updated the Therapeutic Area Head on the Celgene Therapeutic Area Head Signature Page.
- Section 16.3 Product Quality Complaint was also added per new language in the protocol template.
- Appendix I: List of Abbreviations and Definitions of Terms was also updated to include new terms or delete terms that are no longer used within the protocol.

1. JUSTIFICATION FOR AMENDMENT

This protocol is being amended to address Institutional Review Board (IRB) and Principal Investigator comments which have been endorsed by the Study Steering Committee.

Significant changes included in this amendment are summarized below:

- Primary objective wording was updated to remove the text "the most recent" treatment with a prior injectable hypomethylating agent (iHMA) for MDS to provide clarity that subjects in this trial need to have failed all prior treatments with iHMA and not just "the most recent" treatment. There is no impact expected regarding study population or outcome. Also, please note that this clarification does not change the overall primary objective and no text changes were needed per Section 2.1 Primary Objective.

  Revised sections: Protocol Summary, Section 4.1.3 Randomized Treatment Phase, Section 6.1.1 MDS Diagnosis, WHO and FAB Classifications and IPSS (-R) Risk Classification, and Section 7.2 Inclusion Criteria (criterion number 4).

- Updates were made to detail that the futility analysis may be performed earlier in Stage 1 if 3 or more responders are observed prior to the enrollment of 16 subjects. This update will not change what was originally intended for the futility analysis, but is intended to expedite subject enrollment in the event we do have early responders. Also, to emphasize, we will wait for the last subject's response result in Stage 2 to perform the final overall analysis (rate of response) for that specific cohort. Each of the 4 cohorts will be analyzed separately.

  The protocol language will read as follows:

  "The randomized treatment phase will be conducted in 2 stages, with a futility assessment planned at the completion of Stage 1 to determine whether the null hypothesis (H0: p <12.5%) can be rejected with 3 or more responses in Stage 1. If 3 or more responses have been observed before the end of Stage 1, the planned futility assessment may be performed earlier than at the completion of Stage 1 to confirm the finding of responses.

  This earlier analysis will replace the futility analysis planned at the completion of Stage 1. This earlier futility assessment will have the same integrity as the futility assessment planned at the completion of Stage 1. An analysis will be performed at the completion of Stage 2 to estimate the overall response rate of treatment of all the subjects in the cohort".

  Revised sections: Protocol Summary, Section 4.1 Study Design, and Section 10.1 Overview.

  Also, protocol language will read as follows:

  "A subject is considered evaluable for response once they have one cycle of treatment with a maximum of 6 cycles of treatment".

  Revised section: Section 4.1.3 Randomized Treatment Phase

- The enrollment period and total trial duration were extended due to the length of the CC-486 safety run-in, which required the enrollment and monitoring of additional subjects due to gastrointestinal intolerability. Enrollment was extended from "approximately 24

months" to "approximately 39 months and the total trial duration was updated to change "approximately 36 months" to "approximately 47 months".

Revised sections: Protocol Summary and Section 4.3 Study Duration.

- Updated the section reference from Section 8.2.5 to Section 4.1.3 for those who derive benefit from treatment with investigational product (IP) as Section 4.1.3 better defines this item.

  Revised sections: Protocol Summary and Section 8.2 Treatment Administration and Schedule.

- Updates were made to remove references to specifically defined adverse events of special interest (AESIs) and to instead refer to the Durvalumab Investigator's Brochure, Section 5.4.2 Summary of Risks. This change was made as durvalumab safety profile is still evolving and AESIs are subject to change.

  Protocol Summary, Section 4.1.3 Randomized Treatment Phase, Section 4.1.5.1. Follow-Up in Subjects Receiving CC-486 Monotherapy, Section 4.1.5.2 Follow-up in Subjects Receiving Durvalumab/CC-486 Combination Therapy, Section 6.7 Safety, Section 6.13 Discontinuation, and Section 6.14 Follow-up.

- Provided clarity that 16 subjects "per cohort" will be accrued in Stage 1 and not 16 subjects total and also for 25 additional subjects accrued "per cohort" in Stage 2 for a total of 41 subjects "in each cohort".

  Revised sections: Protocol Summary and Section 10.3 Sample Size and Power Considerations.

- Updated to include durvalumab data per the current Durvalumab Investigator's Brochure, Edition 10.

  Revised sections: Section 1.3 Durvalumab (MEDI4736), Section 1.3.1 Durvalumab Experience in Solid Tumors, and Section 1.3.2 Durvalumab Experience in MDS.

- Updated to include a timeframe for availability for documentation. If documentation of myelodysplastic syndrome (MDS) diagnosis, World Health Organization (WHO)/French-American-British (FAB) classification and International Prognostic Scoring System (IPSS)/IPSS-Revised (-R) risk categorization is available "and within 2 months of screening", results of central review are not required prior to enrollment of the subject in the study.

  Revised sections: Section 4.1.1. Screening Phase, Table 2 Table of Events, and Section 6.1.15 Bone Marrow Aspirate, Biopsy, and Peripheral Blood Smear.

- Based on the outcome of the CC-486 safety run-in, the CC-486 starting dose was lowered from 200 mg BID, 21/28 day to 100 mg BID, 21/28 day for the combination safety run-in therapy and the Phase 2 CC-486 monotherapy.

  The dose levels in Table 1 were updated to "0 to -3" instead of specifically noting a "starting dose" of 200 mg BID, 21/28 only.

  Also, clarification is added to state that the safety run-in for CC-486 monotherapy has been completed as of December 2016.

Revised sections: Sections 4.1.2 Safety Run-in, Table 1: CC-486 Dose Levels for Safety run-in, and Table 3: Dose Modification Steps.

- Updated text to include "Please refer to Section 4.1.2.1 for CC-486 related dose-limiting toxicity criteria". Criteria was defined for durvalumab dose-limiting toxicities and wanted to guide the reader to the previous section for CC-486 specific dose-limiting toxicities (for their reference) as this is combination therapy investigating both CC-486 + durvalumab.

  Revised section: Section 4.1.2.2 Durvalumab/CC-486 Combination Therapy Dose-Limiting Toxicity.

- Additional sample collections are allowed if the site would like to work-up the subject for progression. Footnote p was updated to include that unscheduled sample collections are also permitted if disease progression is suspected.

  Revised section: Table 2: Table of Events

- The window for inclusion criterion number 5 which was originally 12 weeks was increased to 16 weeks due to the difficulty for sites to gather prior subject data with regard to prior transfusions, prior iHMA treatments, etc. which potentially would come from outside hospitals or other treating institutions. Alignment was gained with the Study Steering Committee to extend this window from 12 to 16 weeks.

  Also, the additional text "Given this timeframe, subjects may begin screening after the last dose of prior injectable HMA" was added for clarity on when subjects could begin screening in relation to their last HMA dose.

  Revised sections: Section 6.1 Screening, Section 6.1.4 Prior Medications and MDS Treatments, and Section 7.2 Inclusion Criteria (criterion number 5).

- Urine collection is not required on Cycle 1 Day -1. This text should have been removed in Amendment 1. Please note that no Cycle 1 Day -1 urine samples have been collected to date.

  Revised section: Section 6.1.10 Urinalysis

- Removed reference to collecting "corresponding normal range(s)" in the case report form (CRF). Local laboratory ranges will be collected in the electronic CRF (eCRF), however the corresponding normal ranges are not collected via CRF.

  Section 6.7.7 Hematology and Serum Chemistry Laboratory Evaluations

- Reference to Section 8.2.2.1 is added for clarity for overnight fasting details and correction was made of a typographical error for Cycle 2 blood collections for durvalumab as Cycle 1 Day 1 (C1D1) was meant to be C"2"D1.

  Revised section: Section 6.10 Pharmacokinetics

- Electrocardiogram is added in the assessments at discontinuation.

  Revised section: Section 6.13 Discontinuation

- Contraceptive methods for females was updated per IRB recommendations and to remain in line with the Clinical Trial Facilitation Group (CTFG) Recommendations related to

Contraception and Pregnancy Testing in Clinical Trials (available at the Heads of Medicine Agencies [HMA] website).

Revised section: Section 7.2 Inclusion Criteria (criterion number 8)

- Contraceptive requirements for male participants is updated per the Durvalumab Informed Consent Risk language.

  Revised section: Section 7.2 Inclusion Criteria (criterion number 9)

- Included "or" between the two definitions outlined for rapidly-progressing MDS to provide clarity that both definitions do not have to be met but instead one definition only could constitute rapidly-progressing MDS.

  Revised section: Section 7.3 Exclusion Criteria (criterion number 1)

- Removed "or autologous" stem cell transplant per recommendations from the Study Steering Committee and Principal Investigators. Autologous stem cell transplant should not apply as low intensity conditioning or post-transplant immunosuppressive therapies are not needed as subjects receive their own cells in this type of transplant.

  Revised section: Section 7.3 Exclusion Criteria (criterion number 3)

- Added "at any time in the subject's prior history" to provide clarity that no time window is required and that prior exposure to "oral" decitabine or other "oral" azacitidine, or ongoing response (per International Working Group [IWG] 2006) to treatment with azacitidine for injection or decitabine can be at any time in the subject's history.

  Revised section: Section 7.3 Exclusion Criteria (criteria numbers 4 and 5)

- Added "planning to become pregnant" to clarify that females who plan to become pregnant will be excluded from this trial.

  Revised section: Section 7.3 Exclusion Criteria (criterion number 16)

- Removed "disseminated intravascular coagulation" (DIC) per the Study Steering Committee recommendation that any prior history of DIC should not preclude subjects from enrolling into this trial. DIC is a transient condition and if resolved would not lead to any sequelae that would prevent the subject from qualifying for this trial.

  Revised section: Section 7.3 Exclusion Criteria (criterion number 21)

- Added exclusion of myeloproliferative neoplasms (MPN) and chronic myelomonocytic leukemia (CMML) to provide clarity that these subjects do not have MDS and should explicitly be excluded from the trial.

  Revised section: Section 7.3 Exclusion Criteria (criterion number 26)

- Updated the list of all discontinuation reasons to align with the current CRFs.

  Revised sections: Section 8.2.7 Discontinuation and Section 12 Discontinuations

- Updated that adverse events (AEs) will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of CC-486, 90 days after the last dose of durvalumab, "or until the Treatment Discontinuation Visit, whichever is later as well as acute myeloid leukemia (AML) cases" to clarify that adverse events also

need to be collected until treatment discontinuation as well as the need to report cases of AML.

Revised sections: Section 11.1 Monitoring, Recording, and Reporting of Adverse Events and Section 11.5 Reporting of Serious Adverse Events

- Updated language per the current Durvalumab Investigator's Brochure, Edition 10 regarding AESIs. Sections 11.7.2, 11.7.3, 11.7.4 and 11.7.5 were removed to align with the current Durvalumab Investigator's Brochure, Edition 10 and because the durvalumab safety profile is still evolving and AESIs are subject to change.

  Revised section 11.7 Adverse Events of Special Interest

- Removed 1 reference (Oganesyan, 2008) as data was updated per the current Durvalumab Investigator's Brochure, Edition 10.

  Revised section: Section 18 References

- Changed the abbreviation for partial response (PR) from partial "remission" to partial "response" to align with terminology used in Section 3.1 Primary Endpoint as well as added additional abbreviations.

  Revised section: Appendix I: List of Abbreviations and Definitions of Terms

The amendment also includes other minor clarifications and corrections:

- Change of Medical Monitor
- "Patient" has been changed to "subject" in applicable instances throughout the protocol amendment
- All references to "study drug" have been updated to "IP"
- International Council for Harmonisation definition was updated throughout text
- Updated the toxicity management guidelines and risk language provided for durvalumab from the current Durvalumab Investigator's Brochure, Edition 10.

  Revised sections: Table 5: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events, Table 6: Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions, and Table 7: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

1. JUSTIFICATION FOR AMENDMENT

Rationale for the amendment:

While injectable hypomethylating agents (azacitidine for injection and decitabine) remain the standard of care in the treatment of International Prognostic Scoring System (IPSS) higher-risk myelodysplastic syndrome (MDS), as many as half of affected patients do not respond to treatment, and nearly all those who do respond will eventually relapse. Upon failure of treatment with azacitidine for injection and/or decitabine, the prognosis for patients with higher-risk disease is dismal, with median overall survival on the order of 4-6 months. Similarly, injectable hypo-methylating agents (iHMAs) are approved for treatment of IPSS lower-risk MDS in some countries, and while there are few data to characterize outcomes in lower-risk disease following failure of these agents, prognosis is poor and for patients who are not eligible for allogeneic stem cell transplant (ASCT), no proven treatment options currently exist.

The goal in treating this population and in evaluating new potentially therapeutic options is to capture or recapture hematologic response or hematologic improvement to reduce the rate of disease progression and acute myeloid leukemia (AML) transformation, and to prolong survival. Despite active interest in the post-HMA setting among researchers, there remains a critical unmet medical need.

Cancer and Immune Function

The importance of the immune system in cancer development and progression has been recognized during the past decade. Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immune-competent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines. The local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity. The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or costimulation, or by suppressing immunosuppressive factors, cells, or messages.

Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers. Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may

control or even eliminate tumors. Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), PD-1, and PD-L1 have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in non-small-cell lung cancer (NSCLC), and prostate cancer.

The PD-1 receptor, in conjunction with receptor ligands PD-L1 and PD-L2, functions to regulate the immune system primarily by down regulating signals of the T-cell receptor. PD-L1 expressed on tumor cells binds to PD-1 on T-cells which leads to down regulation of T-cell activity and allows tumor cells to evade the immune response.

Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with MDS or AML. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors. Studies in mouse models of transplantable tumors have demonstrated that manipulation of costimulatory or co-inhibitory signals can amplify T-cell responses against tumors. This may be accomplished by blocking co-inhibitory molecules such as CTLA-4 or PD-1 from binding with their ligands, B7 or B7-H1 (PD-L1).

PD-L1 expression is present in MDS and AML, with increased expression observed in advanced disease. In addition, there has been evidence to suggest that PD-L1 is upregulated in myeloblasts in MDS subtypes.

In addition, in MDS subtypes, PD-L1 expression on myeloblasts has been associated with MDS transformation to AML. Myeloid leukemia cell lines that were treated with the hypomethylating agent decitabine were shown to have an upregulation of PD-L1 expression. Upregulation ($\geq$ 2 fold) of PD-L1 has been observed in 25% of AML CD34+ samples, 33% of PD-L2, and 22% of PD-1. PD-1 signaling may be involved in MDS pathogenesis and resistance mechanisms to azacitidine; therefore, combined blockade of this pathway can be a potential therapy in MDS and AML.

Based on this information, a rationale exists for evaluating durvalumab in combination with azacitidine in subjects with MDS and AML.

Durvalumab is a human immunoglobulin G (IgG)1 kappa mAb directed against human PD-L1. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and cluster of differentiation 80. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity.

Study CD-ON-MEDI4736-1108 is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, pharmacokinetics (PK), immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. As of 21 Aug 2014, 408 subjects across 8 tumor types (NSCLC, squamous cell carcinoma of the head and neck, pancreatic adenocarcinoma, uveal melanoma, cutaneous melanoma, gastroesophageal cancer, triple-negative breast cancer, and

hepatocellular carcinoma [hepatitis B virus and hepatitis C virus positive]) have received durvalumab 10 mg/kg every 2 weeks (Q2W) for a median of 6 doses.

Partial efficacy data are available as of 21 Aug 2014. In this study, 352 of 408 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response analysis, which included subjects who had at least 12 weeks of follow-up as of the data cutoff date, measurable disease at baseline, and at least 1 follow-up scan (included discontinuations due to progressive disease [PD] or death prior to first follow-up scan). Early (5 weeks) and durable (56+ weeks) activity were observed across multiple tumor types. Disease control rate at 12 weeks (DCR-12w) was 33% (115/352 subjects) and objective response rate (ORR) was 10% (36/352 subjects) across the 8 tumor types. Greater DCR-12w (47% vs 28%) and ORR (22% vs 5%) were observed in subjects with PD-L1-positive versus PD-L1-negative tumor. Responses are ongoing in 92% of subjects (33/36) with an objective response (OR).

Durvalumab is being evaluated in MDS after iHMA treatment. CCI [redacted]

Despite active interest in the post-HMA setting among researchers, there remains a critical unmet medical need. The current study is being amended to additionally evaluate a new potentially therapeutic option, durvalumab in combination with CC-486, in an effort to capture or recapture hematologic response or hematologic improvement, to reduce the rate of disease progression and AML transformation, and to prolong survival.

Significant changes included in this amendment are summarized below:

An additional investigational product (IP), anti-PD-L1 monoclonal antibody, durvalumab (MEDI4736) in combination with CC-486 (combination therapy), will be evaluated in this study in addition to the evaluation of CC-486 as monotherapy. The changes in the protocol are being made to accommodate this additional arm of combination therapy.

The Introduction (Section 1) now includes a description of durvalumab (Section 1.3) including experience in MDS. Study Rationale (Section 1.4) was changed to include information on cancer and immune function, immune checkpoint inhibition CCI [redacted] and durvalumab fixed dosing regimens.

The primary objective of the study (Title Page, Protocol Summary and Section 2.1) remains the same except for the addition of combination therapy. The original secondary objectives also remain the same except for the addition of combination therapy. An additional secondary objective was added to evaluate the pharmacokinetics of the durvalumab and CC-486 combination. CCI [redacted]

CCI [redacted]

The study design (Protocol Summary, Section 4) and study design rationale (Section 4.2) has been changed to accommodate the addition of the combination therapy. The study design now includes a safety run-in: a 3+3 design for CC-486 monotherapy followed by a 3+3 design with combination therapy to evaluate safety and tolerability. Dose limiting toxicity was defined for monotherapy and for combination therapy. The previous randomized treatment phase was changed to add the additional arm of combination therapy. Section 4.1.3 was updated to state that once the CC-486 dose and schedule in the safety-run in of a treatment arm is identified, enrollment for Stage 1 of the treatment phase may begin. A pharmacokinetic sub-study (Section 4.1.4 and 6.10) was added that will collect samples from 10-12 evaluable subjects randomized to the combination treatment arm. Subjects participating in the pharmacokinetic sub-study will receive CC-486 on Day -1 of Cycle 1 (Section 6.3, Section 6.10, Section 8.2).

The previous study design (Figure 1) and the amended study design including the run-in phase (Figure 2 and 3) are attached. The follow-up phase is extended from 28 days to 90 days for the combination therapy.

Study populations (Protocol Summary, Section 7.1) has been amended to include additional subjects for treatment in the safety run-in and in the combination arm. At least 6 subjects will be treated in the safety run-in phase, utilizing the standard 3+3 design for the monotherapy and then for the combination therapy. The Stage 1 randomized treatment will include 64 subjects: approximately 32 with stable disease and 32 with progressive disease. If there are 3 or more responses in any arm, that arm with enroll 25 additional subjects in Stage 2. The total number of subjects in the randomized treatment phase will range from 64 to 164 subjects.

The enrollment period (Protocol Summary, Section 4.3) for this study has been increased and is expected to last approximately 24 months. The treatment and follow-up phases of study are expected to conclude approximately 12 months after the last subject is enrolled. Therefore, the total duration of the study is expected to be approximately 36 months.

Inclusion criteria was amended to include the signing of an additional CCI [redacted] CCI [redacted] and the exclusion criteria (Section 7.3) was amended to add exclusions appropriate to ensure safety and exclusions of conditions that would confound the ability to interpret the data of subjects receiving durvalumab including subjects who received previous treatments similar to durvalumab.

Study treatment (Title Page, Protocol Summary, Section 6.5 now Section 6.6, Section 8, Section 7.3, and Section 9.2) was amended to add the following information for durvalumab: description, dosing and administration, IP dispensation and guidelines for toxicity management and overdose. Prohibited medications was expanded to add immunosuppressive agents and live attenuated vaccines.

Statistical analysis (Protocol Summary, Section 10) now refers to the 2-arm study with the addition of the combination treatment. Sample size and power considerations, primary efficacy analysis, CCI [redacted] were changed to reflect the addition of the combination therapy arm.

Safety assessments and adverse events (Protocol Summary, Table of Events, Section 6.6 now Section 6.7 and Section 11), and adverse events of special interest were added primarily to reflect those additional events that are specific to durvalumab, e.g., hepatic function abnormality, pneumonitis, infusion reactions and hypersensitivity. Appropriate safety assessments were added including infusion monitoring and 12-lead ECG at study discontinuation.

Other significant changes and rationale for those changes:

Concomitant medications (Section 6.1.4, Section 6.6.7 now 6.7.9, Section 9, Table 1 footnote) All prescription, over-the-counter, or herbal medications and therapeutic procedures received within ~~12~~ 4 weeks (28 ~~84~~ days) prior to the first dose of IP, until 28 days after the last dose of the IP (or until the treatment discontinuation visit, whichever period is longer) must be recorded on the appropriate CRF page.

Rationale: Medications discontinued more than 28 days prior to the first dose of IP will be unlikely to impact the study. Treatments for MDS are gathered outside of that time frame.

Coagulation parameters will be collected at baseline (Table 1 now Table 2: Table of Events and Section 6.1.5).

Rationale: Collection of coagulation parameters has been added as an additional safety measure.

Amylase and lipase will now be added to serum chemistries as well as thyroid function tests (Protocol Summary, Section 4.1.3, Table of Events, Section 6.1.13, Section 6.7, Section 6.14)

Rationale: Collection of amylase, lipase and thyroid function tests have been added as additional safety measures.

A urine sample should be collected prior to IP administration on Day 1 of every 3rd treatment cycle (i.e. Cycles 3, 6, 9, etc), treatment discontinuation and safety follow-up, and sent to central lab for analysis (Protocol Summary, Section 4.1.3, Table of Events, Section 6.1.10, Section 6.7, Section 6.13 and Section 6.14).

Rationale: Urine monitoring time points have been added as an additional safety measure.

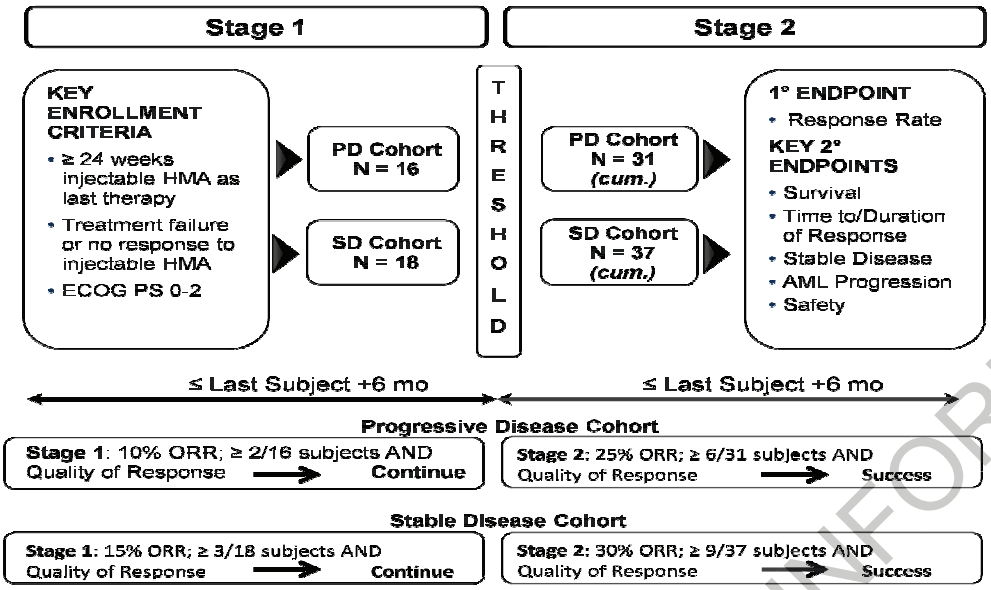
IVRS (Interactive Voice Response System) was changed to IRTS (Interactive Response Technology System).

Rationale: This change was provided by Endpoint, our IRTS vendor.

CCI

[redacted]

Figure 1: Overall Study Design Prior to Amendment



Key: AML = acute myeloid leukemia; Cum = cumulative; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HMA = hypomethylating agent; mo = month; ORR = overall response rate; PD = progressive disease; SD = stable disease

Figure 2: Safety Run-in Phase Study Design in Protocol Amendment

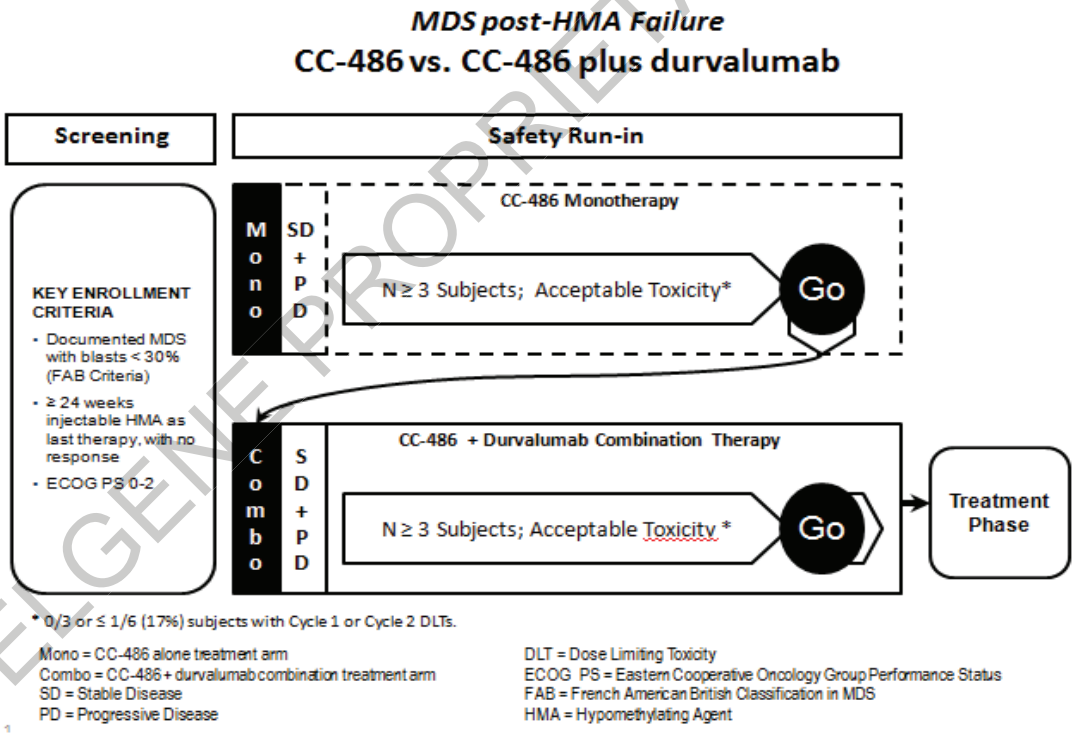


Figure 3: Randomized Treatment Phase Study Design in Protocol Amendment