DISCLOSURE

REDACTED PROTOCOL AMENDMENT 3

MEDI4736-MDS-001

A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF AZACITIDINE SUBCUTANEOUS IN COMBINATION WITH DURVALUMAB (MEDI4736) IN PREVIOUSLY UNTREATED SUBJECTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (MDS) OR IN ELDERLY (≥ 65 YEARS) ACUTE MYELOID LEUKEMIA (AML) SUBJECTS NOT ELIGIBLE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FUSION HR MDS/ELDERLY AML 001 STUDY

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A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF AZACITIDINE SUBCUTANEOUS IN COMBINATION WITH DURVALUMAB (MEDI4736) IN PREVIOUSLY UNTREATED SUBJECTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (MDS) OR IN ELDERLY (≥ 65 YEARS) ACUTE MYELOID LEUKEMIA (AML) SUBJECTS NOT ELIGIBLE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

FUSION HR MDS/ELDERLY AML 001 STUDY

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PROTOCOL SUMMARY

Study Title

A Randomized Multicenter, Open-label, Phase 2 Study Evaluating the Efficacy and Safety of Azacitidine Subcutaneous in Combination With Durvalumab (MEDI4736) in Previously Untreated Subjects with Higher-Risk Myelodysplastic Syndromes (MDS) or in Elderly (≥ 65 years) Acute Myeloid Leukemia (AML) Subjects Not Eligible for Hematopoietic Stem Cell Transplantation (HSCT).

Indication

Treatment of subjects with untreated myelodysplastic syndromes (MDS), Revised International Prognostic Scoring System (IPSS-R) intermediate risk (in combination with more than 10% bone marrow (BM) blasts or poor or very poor IPSS-R cytogenetic risk), IPSS-R high and IPSS-R very high risk, not eligible for HSCT.

Treatment of previously untreated elderly (≥ 65 years) acute myeloid leukemia (AML) subjects not eligible for HSCT with intermediate or poor cytogenetic risk status.

Objectives

Primary Objective:

Efficacy:

- Evaluate the efficacy of subcutaneous (sc) azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population.

Secondary Objectives:

Safety:

- Assess the safety and tolerability of subcutaneous (sc) azacitidine in combination with durvalumab compared with subcutaneous azacitidine alone in the defined study population.

Pharmacokinetics:

- To assess the pharmacokinetics (PK) of durvalumab when given in combination with subcutaneous azacitidine in the defined study population.

Study Design

This is a randomized, multicenter, open-label, Phase 2 study evaluating the efficacy and safety of subcutaneous azacitidine in combination with durvalumab in two separate cohorts. Cohort 1 comprises subjects with previously untreated MDS IPSS-R intermediate risk (in combination with more than 10% bone marrow blasts or poor or very poor IPSS-R cytogenetic risk), IPSS-R high and IPSS-R very high risk, who are not eligible for HSCT. Cohort 2 comprises subjects with previously untreated AML who are elderly (≥ 65 years) and not eligible for HSCT, with intermediate or poor cytogenetic risk.

Subjects will be randomized (1:1 ratio) to receive one of the two treatment arms:

- Arm A (subcutaneous azacitidine plus durvalumab)

- Arm B (subcutaneous azacitidine alone)

The randomization process will aim to balance prognostic factors between study arms. For both cohorts (MDS and AML), subjects will be randomized and stratified according to their cytogenetic risk:

- Intermediate versus poor for AML (Appendix J),
- Very good, good and intermediate versus poor and very poor for MDS (Appendix H).

The randomized study will be conducted in 2 stages, with an interim analysis for futility purpose for each of the 2 disease cohorts as outlined in Section 9. The primary analysis will follow completion of Stage 2 (ie after all subjects have completed 6 cycles and had disease assessment) with additional analyses conducted approximately 12 months after the last subject is enrolled, as described in Section 9. In addition an early safety monitoring will be performed using approximately the first 12 subjects randomized.

Study Population

Approximately 182 eligible and evaluable subjects will be included in this study.

Eligible subjects for the study will require a documented diagnosis of either AML or MDS as defined in Section 4, and will be assigned to either the AML or MDS cohort based on the central laboratory diagnosis confirmation. Approximately 72 subjects will be included in the MDS cohort and approximately 110 subjects in the AML cohort.

Length of Study

The enrollment period for this study is expected to last approximately 15 months. The treatment and follow-up periods are expected to conclude approximately 12 months after the last subject is randomized. Therefore, the total duration of the study is expected to be approximately 27 months, from first subject enrolled until the last subject last visit.

Subjects will undergo screening procedures over a period of up to 35 days following the signing of their informed consent form (ICF). Eligible subjects will continue to the treatment part of the study where they will receive investigational product (IP) for at least six 28-day treatment cycles. Those who demonstrate benefit from treatment may continue the IP beyond Cycle 6 until loss of that benefit or unacceptable toxicity, or withdrawal of consent (Section 7.2.5).

All subjects will have a Treatment Discontinuation Visit within 7 days after discontinuation of study treatment. Subjects are to return to the study site 28 days after the last dose of subcutaneous azacitidine and 90 days after the last dose of durvalumab for Safety Follow-up Visits. After this visit, subjects will be contacted by telephone every 3 months in the follow-up phase of the study.

The End of Trial is defined as either the date of the last subject last visit for the completion of posttreatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date. See Section 3.3.

Study Treatments

Subjects will be randomized 1:1 to receive either:

Treatment Arm A: Subcutaneous azacitidine (75 mg/m^2 for 7 days every 4 weeks [Q4W]) in combination with intravenous (IV) durvalumab at a dose of 1500 mg on Day1 Q4W,

Or

Treatment Arm B: Subcutaneous azacitidine alone at the dose of 75 mg/m^2 for 7 days Q4W.

Early safety monitoring and a comparative safety evaluation will be performed on approximately the-first 12 subjects randomized to the study (Section 3.2.2.2).

For toxicities 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 7.2.2.2. Dose reduction for durvalumab is not permitted. The management of the toxicity due to azacitidine is described in Section 7.2.2.1.

Subjects should receive at least 6 cycles of treatment; however, subjects may be discontinued from treatment at the Investigator's discretion prior to reaching the recommended minimum number of cycles. Upon completing 6 cycles, subjects who benefit from treatment may continue IP until loss of that benefit, disease progression or other treatment discontinuation criterion is met (see Section 7.2.5).

Overview of Key Efficacy Assessments

Subjects' disease status will be assessed based on available clinical and laboratory assessments (bone marrow aspirate [BMA]) at the end of Cycle 3, 6 and every 3rd treatment cycle thereafter. Subjects who satisfy one of the continuation criteria listed below may continue on to Cycle 7 and beyond.

Continuation criteria for MDS cohort:

- Overall response to treatment: complete remission (CR), marrow complete remission (mCR), partial remission (PR) as per the International Working Group (IWG) criteria for MDS (Cheson, 2006), or
- Red blood cell (RBC) transfusion-independence for at least 56 consecutive days, or
- Any hematologic improvement (HI) as per the IWG criteria for MDS (Cheson, 2006), or
- Any other clinical benefit, including no evidence of progressive disease (PD).

Continuation criteria for AML cohort:

- Overall response to treatment: Complete Remission (CR) or Complete Remission with incomplete blood count recovery (CRi) per modified IWG response criteria for AML (Cheson, 2003), or
- Any other clinical benefit including no evidence of progressive disease (PD).

Disease diagnosis for all subjects will be confirmed by the central laboratory prior to randomization, based on blood samples, bone marrow aspirate and biopsy (at screening only).

Bone marrow samples (aspirate and/or biopsy), along with a peripheral blood smear and pertinent clinical information will be submitted for review to an independent pathologist/cytogeneticist to provide consistency for determination of disease classification, assessment, 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 Section 5 (Table of Events).

CCI [redacted]

Overview of Key Safety Assessments

- Adverse Events(AEs) including adverse events of special interest (AESIs)
- 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 (includes amylase and lipase)
- Thyroid function tests
- Concomitant medications, therapies, and procedures
- Pregnancy testing (for females of childbearing potential [FCBP] only)
- Electrocardiogram (ECG)
- Urinalysis

Azacitidine and durvalumab are generally well tolerated without anticipated overlapping toxicities. Azacitidine causes well described gastrointestinal and hematologic AEs in the form of cytopenias and durvalumab has a low frequency of immune-mediated adverse events similar to other immune checkpoint agents (See section 1.4).

Overview of Pharmacokinetics Assessments

Blood samples for PK assessment of durvalumab will be collected in all subjects receiving combination therapy.

CCI [redacted]

CCI [redacted]

Statistical Methods

This is a randomized Phase 2, multicenter, open-label study with 2 separate, parallel disease cohorts (MDS and AML).

The study will be conducted in 2 stages for each disease cohort (Section 9.3). Subjects will be randomized with 1:1 ratio to receive subcutaneous azacitidine monotherapy or subcutaneous azacitidine in combination with durvalumab.

The randomization procedure will be accomplished by a validated Interactive Response Technology (IRT). At randomization, subjects will be stratified by cytogenetic risk, very good, good and intermediate versus poor or very poor for MDS cohort, and intermediate versus poor for AML cohort.

In the MDS cohort, the primary efficacy endpoint is the overall response rate (defined as CR, mCR, PR, and/or HI) as determined using the IWG 2006 response criteria for MDS. The null hypothesis of the response rate (H0 : $p \leq 36\%$) will be tested against the alternative hypothesis of the response rate (H1 : $p \geq 72\%$) with a type I error rate of 5% and 90% power. A total of 72 subjects will be randomized. An interim analysis for futility purpose will be conducted when 30 subjects have completed 6 cycles of treatment (See Section 9.3.1).

In the AML cohort, the primary efficacy endpoint is overall response rate (CR or CRi) based on modified IWG 2003 response criteria for AML. The null hypothesis of the response rate (H0 : $p \leq 25\%$) will be tested against the alternative hypothesis of the response rate (H1 : $p \geq 50\%$) with a type I error rate of 5% and 80% power. A total of 110 subjects will be randomized. An interim analysis for futility purposes will be conducted when 50 subjects have completed 6 cycles of treatment (see Section 9.3.2).

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1. INTRODUCTION

1.1. Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) is an umbrella term that encompasses a heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. Myelodysplastic syndromes is typically characterized by bone marrow (BM) 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.

Allogeneic bone marrow transplantation has been effective, both in subjects 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 subjects 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 for MDS (NCCN, 2016).

Higher-risk MDS for this study is defined according to Revised International Scoring System (IPSS-R) (Greenberg, 2012): High and Very High with a median survival of 1.6 and 0.8 years respectively, and the subpopulation of the Intermediate Risk category with poor and very poor cytogenetics with median survival of 1.5 and 0.7 years respectively or a blast count > 10% (survival 1.3 years). This is corresponding to the previously used IPSS (Greenberg, 1997) intermediate-2 (INT-2) and High-Risk Group with a median survival of 1.1 and 0.4 years, respectively.

For subjects diagnosed with, or progressing to, higher-risk disease, the standard of care is treatment with a hypomethylating agent (HMA): azacitidine for injection or decitabine. Injectable HMAs can produce hematologic response or improvement in approximately half of treated subjects, but responses are transient and responding disease will eventually relapse (Sekeres 2014b, Grinblatt, 2008; Lyons, 2009; Musto, 2010; Silverman, 2002).

1.2. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive, clonal myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myeloblasts in BM and/or blood. Acute myeloid leukemia is a life-threatening disease that primarily affects older adults, with a 5-year survival rate of 19% (Visser, 2012). More than half of the subjects with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67 to 69 years (Colita, 2011; Pollyea, 2011; Smith, 2011). Acute myeloid leukemia is the most frequent form of leukemia, accounting for approximately 25% of all leukemias in adults in the Western world (Deschler, 2006). Acute myeloid leukemia can arise de novo, through transformation of existing myelodysplasia, or be secondary to previous therapy (eg, cytotoxic chemotherapy). It is

estimated that 35% to 40% of subjects with MDS will go on to develop AML, with the disease often refractory to current therapy (Silverman, 2002). Pre-existing myelodysplastic or myelo-proliferative disorders are common in older subjects with AML, occurring in 24% to 40% of cases (Gajewski, 1989). Therapy-related AML accounts for about 5% to 10% of all cases (Leone, 1999). The prognosis for these subjects is considerably worse than that for subjects with primary AML (Löwenberg, 1999). As previously discussed, AML is more common in elderly subjects than in younger subjects; furthermore, the prognosis for elderly subjects is far less favorable, with only 5% of subjects achieving a 5-year survival compared to 30% in subjects aged 30 to 64 years (Visser, 2012). Overall, the elderly subject with AML has a higher incidence of unfavorable cytogenetics, molecular mutations, secondary AML (related to previous anticancer therapy or prior myelodysplastic diseases), comorbidities, and generally poorer performance characteristics.

Treatment decisions in elderly subjects with AML are complex and often guided by health status, consideration of quality of life (QoL) and subject preferences. Once AML has been diagnosed in elderly subjects, based upon the factors described above, a decision must be made for intensive chemotherapy and/or hematopoietic stem cell transplantation (HSCT), low-intensive chemotherapy, a clinical trial, or supportive care alone (Döhner, 2010). Hematopoietic stem cell transplantation is rarely used in subjects older than 65 years of age and is reserved for the fit subjects with a good prognosis and a matching donor after induction therapy.

Intensive induction chemotherapy is recommended for older subjects with good performance status (PS), minimal organ dysfunction or comorbidity, and favorable cytogenetics. Intensive induction chemotherapy is the only treatment option that has demonstrated a chance of long-term survival in elderly AML subjects with median survivals from 7 to 12 months; however, it also carries a high risk of induction-related mortality (10% to 30%) (Burnett, 2007; Deschler, 2006; Dombret, 2008; Estey, 2007; Klepin, 2014).

Generally subjects over 75 years old, or those at least 65 years old with PS scores ≥ 2, with comorbidities or with complex cytogenetic abnormalities (Milligan, 2006; O'Donnell, 2012) are considered to be ineligible for intensive chemotherapy.

Low-dose cytarabine is considered the standard treatment for subjects ineligible for intensive chemotherapy and who also have nonadverse cytogenetics. The complete remission (CR) rates with low-dose cytarabine are 18% to 22%, with early deaths (within 60 days of the start of chemotherapy) reported between 22% to 28% (Yoon, 2013).

Azacitidine and decitabine are both recommended as alternative treatment options in the NCCN guidance for AML (NCCN, 2015) to intensive chemotherapy or low-dose cytarabine and best supportive care (BSC) for subjects at least 60 years of age.

1.3. Azacitidine

Azacitidine is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. Azacitidine has strong in vitro and in vivo antileukemic activity and the ability to induce differentiation at lower concentrations in hematopoietic and nonhematopoietic 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.

1.3.1. Clinical Safety Experience with Azacitidine

As of 18 May 2016, approximately 19,685 subjects have been treated with azacitidine in clinical studies, with 2,049 in the Celgene development program worldwide (1,144 with azacitidine injectable, 717 with azacitidine oral, and 192 with injectable and oral azacitidine (please note that 3 subjects from AZA PH US 2007 CL005 and 1 subject from AZA PH US 2008 CL008 enrolled in roll-over protocol CC-486-GEN-001, are counted only once in the overall total), 8,656 through National Cancer Institute (NCI)-sponsored clinical studies in the US, and an estimated 8,980 in non-Celgene-sponsored studies globally. In addition, it is estimated that cumulative commercial exposure to azacitidine during marketing experience is 273,411 patients. Therefore, overall estimated cumulative exposure to azacitidine during clinical trials and commercial experience is 293,096 patients (Azacitidine Development Safety Update Report [DSUR] #12, data cut-off 18 May 2016).

The most commonly reported adverse reactions with azacitidine treatment were hematological reactions including anemia, thrombocytopenia, neutropenia, febrile neutropenia, and leukopenia, gastrointestinal events including nausea, vomiting, abdominal pain, constipation, and diarrhea, and injection site reactions (with sc administration).

For the most frequently reported treatment emergent adverse events (TEAEs) (≥ 10% of subjects), the highest incidence of first occurrence was observed within Cycles 1 and 2, after which time the frequencies decreased over subsequent treatment cycles. Within the cycle, the hematological events tended to occur across the first 3 to 4 weeks of the cycle, whereas the events associated with the administration of azacitidine tended to occur in the first week. These findings suggested a lack of cumulative toxicity and that adverse events (AEs) of azacitidine attenuate over time.

In general, no clinically relevant differences were seen when the safety data were analyzed for age, gender, or MDS subtypes. The most common adverse reactions can be managed through delays or dose decrease of azacitidine and/or supportive measures.

Adult population with MDS, chronic myelomonocytic leukemia (CMML) and AML (20% to 30% marrow blasts)

The most commonly reported adverse reactions with azacitidine treatment were hematological reactions (71.4 %) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6 %) including nausea, vomiting (usually Grade 1-2), or injection site reactions (77.1 %; usually Grade 1-2).

The most common serious adverse reactions noted from the pivotal study (AZA PH GL 2003 CL001) and also reported in the supporting studies (CALGB 9221 and CALGB 8921) included

febrile neutropenia and anemia. Other serious adverse reactions from these 3 studies included neutropenic sepsis and pneumonia (some with fatal outcome), thrombocytopenia, hypersensitivity reactions, and hemorrhagic events (eg, cerebral hemorrhage, gastrointestinal hemorrhage, and intracranial hemorrhage).

Adult population aged 65 years or older with AML with > 30% marrow blasts

The most commonly reported (≥ 30%) adverse reactions with azacitidine treatment were gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhea (36.9%), (usually Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; usually Grade 1-2) and hematological events, including febrile neutropenia (32.2%) and neutropenia (30.1%) (usually Grade 3-4).

The most common serious adverse reactions (≥ 10%) noted from AZA-AML-001 within the azacitidine treatment arm included febrile neutropenia (25.0%), pneumonia (20.3%), and pyrexia (10.6%). Other less frequently reported serious adverse reactions in the azacitidine treatment arm included sepsis (5.1%), anemia (4.2%), neutropenic sepsis (3.0%), urinary tract infection (3.0%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%), and dyspnea (2.1%).Hemorrhagic and infectious events overall were generally reported at percentages that were slightly greater in azacitidine subjects than supportive care subjects (most frequent events in these categories were epistaxis, hematoma, petechiae, nasopharyngitis, and pneumonia). However, adjusting for different lengths of treatment, event rates overall were similar between the 2 treatment groups; thus, risks were similar for these types of events occurring in both groups. Hepatic and renal TEAEs were reported in a small number of subjects across treatment groups and did not suggest an association of azacitidine treatment with renal or hepatic toxicity.

The safety profile of azacitidine has been well characterized and is based on an extensive amount of subject exposure across a wide range of doses and indications, as well as routes of administration (sc, intravenous [IV], oral). The AE profile is remarkably consistent across studies, with the most common TEAEs consistent with the known pharmacology of the compound, as well as the effects of the underlying disease.

1.3.2. Clinical Experience of Azacitidine in Myelodysplastic Syndromes

Azacitidine has been studied extensively in MDS. The efficacy and safety of azacitidine were studied in an international, multicenter, controlled, open-label, randomized, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001) in subjects with INT-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T) and modified chronic myelomonocytic leukemia (mCMML) according to the French- American-British (FAB) classification system. Refractory anemia with excess blasts in transformation (RAEB-T) subjects (21% to 30% blasts) are now considered to be AML subjects under the current WHO classification system. Azacitidine plus best supportive care (BSC) (n = 179) was compared to conventional care regimens (CCR). Conventional care regimes consisted of BSC alone (n = 105), low-dose cytarabine plus BSC (n = 49) or standard induction chemotherapy plus BSC (n = 25). Subjects were preselected by their physician to 1 of the 3 CCR prior to randomization. Subjects received this preselected regimen if not randomized to azacitidine. As part of the inclusion criteria, subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The primary endpoint of the study was overall

survival. Azacitidine was administered at a subcutaneous dose of 75 mg/m^2 daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1 to 39) and a mean of 10.2 cycles. Within the intent to treat population (ITT), the median age was 69 years (range 38 to 88 years). In the ITT analysis of 358 subjects (179 azacitidine and 179 CCR), azacitidine treatment was associated with a median survival of 24.46 months versus 15.02 months for those receiving CCR treatment, a difference of 9.4 months, with a stratified log-rank p-value of 0.0001. The hazard ratio (HR) for the treatment effect was 0.58 (95% confidence interval [CI]: 0.43, 0.77). The two-year survival rates were 50.8% in subjects receiving azacitidine versus 26.2% in subjects receiving CCR ($p < 0.0001$) (Fenaux, 2009). In this trial the "HI and better" response using IWG 2006 was 36.4% similar to what has been demonstrated in Sekeres (2014) with an ORR (CR, mCR, PR, HI) of 36% after four cycles of azacitidine monotherapy. Data from the AZA-PH-GL-2003-CL-001 survival study with azacitidine in higher-risk MDS subjects found, from analysis of pretreatment bone marrow methylation density, that the overall survival (OS) benefit observed with azacitidine versus 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 OS. Subjects with lower levels of methylation treated with azacitidine had the best OS, suggesting that they may derive greater benefit from azacitidine.

1.3.3. Clinical Experience of Azacitidine in Acute Myeloid Leukemia

Azacitidine has been shown to benefit AML subjects with 20% to 30% blasts and multi-lineage dysplasia based on the results of a subset of 113 adult subjects in Study AZA PH GL 2003 CL 001. Azacitidine was administered subcutaneously (sc) at an initial dose of 75 mg/m²/day for 7 days. The median age was 70 years, 24% of subjects had unfavorable karyotype, and median BM blasts was 23%. The median OS was 24.5 months in the azacitidine arm (n = 55) compared with 16.0 months in the CCR arm (n = 58) (hazard ratio [HR] = 0.47; p = 0.005) (Fenaux, 2010).

Additionally, Goldberg et al reported on 33 subjects 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 OS was 13.2 months in the subjects treated with azacitidine compared with 9.2 months in subjects receiving intensive chemotherapy (Goldberg, 2006).

In addition, the outcome was not significantly different in subjects with an unfavorable karyotype, although the sample size was small. Silverman et al, using WHO-defined AML criteria for diagnosis, reported a median OS of 19.3 months (n = 27) in subjects treated with azacitidine compared with 12.9 months (n = 25) in subjects who received best supportive care (Silverman, 2006).

The efficacy and safety of azacitidine were studied in an international, multicenter, controlled, open-label, randomized, parallel-group, Phase 3 comparative study (AZA-AML-001) in older subjects (≥ 65 years) with newly diagnosed AML with more than 30% BM blasts. Subjects were randomized to azacitidine or CCR. Response was assessed by IWG criteria for AML (Cheson, 2003) and overall response (OR) was defined as CR plus morphologic CR with incomplete blood count recovery (CRi). The median OS was 10.4 months (95% CI = 8.0, 12.7) in the azacitidine group (n = 241) compared with 6.5 months (95% CI = 5.0, 8.6) in the CCR group (n = 247), with a clinically meaningful difference in OS of 3.8 months with azacitidine treatment. The

azacitidine group had a 15% reduced risk of death compared with subjects in the CCR group (HR = 0.85; 95% CI = 0.69,1.03). Although there was a clinically meaningful improvement in median OS, the difference between survival curves based on the log-rank test did not reach the predefined level of significance (log-rank test, with a stratified p = 0.1009) (Dombret, 2015). In a subgroup analysis for subjects with myelodysplasia-related changes the median OS was 12.7 months (95% CI = 7.2, 14.1) in the azacitidine group (n = 75) compared with 6.3 months (95% CI = 4.3, 9.6) in the CCR group (n = 83) log rank p = 0.0357 (Seymour, 2014).

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 subjects (> 70 years of age) respond as well as younger subjects, and failure to respond to prior therapy with erythropoiesis stimulating agents (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).

In the United States (US), azacitidine (Vidaza®) is approved for the treatment of all 5 FAB classification subtypes of MDS: refractory anemia (RA), refractory anemia with ringed sideroblasts (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 nonhematopoietic stem cell transplantation-eligible subjects 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).

In October 2015 the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has approved an expanded indication for the treatment of adult subjects aged 65 years or older with AML who are not eligible for HSCT. The expanded indication now covers subjects who have > 30% myeloblasts according to the WHO classification; previously, the indication covered AML subjects with ≤ 30% blasts.

1.4. Durvalumab (MEDI4736)

Durvalumab is a human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against human programmed death ligand-1 (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 (ADCC) (Oganesyan, 2008).

Refer to the current Investigator's Brochure for further details.

1.4.1. 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.

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Durvalumab half-life is approximately 23 days at doses ≥ 3 mg/kg Q2W (Fairman, 2014).

1.4.2. Durvalumab Experience in Myelodysplastic Syndromes

Study D4190C00007 is an ongoing Phase 1, multicenter, open-label study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of durvalumab in adult subjects with MDS after prior treatment with hypomethylating agents.

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1.5. Study Rationale

1.5.1. Summary/Medical need

Despite the advances based on the use of HMAs, the overall survival in higher-risk MDS (24.5 months) is still insufficient (Fenaux, 2009).

Elderly subjects with AML not eligible for HSCT have a very poor prognosis with an overall survival of 6.5 months with CCR and 10.5 months with azacitidine (Dombret, 2015).

1.5.2. Rationale for Use of PD-1/PD-L1 Inhibition in Myelodysplastic Syndromes/Acute Myeloid Leukemia

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 preneoplastic 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 immune suppressive factors, cells, or messages (Monti, 2005).

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 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 non-small-cell lung cancer (NSCLC) (Brahmer, 2010; Brahmer, 2012; Topalian, 2012; Gordon, 2013), 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 metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 and nivolumab for melanoma and advanced (metastatic) NSCLC whose disease progressed during or after platinum-based chemotherapy. 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. Programmed death ligand-1 (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 subjects 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).

Programmed death ligand-1 (PD-L1) and PD-L2 are expressed on many human lymphomas (Li, 2012; Chen, 2013). Programmed death ligand-1 (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). Programmed death ligand-1 (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).

1.5.3. Rationale for the Combination of Durvalumab with Azacitidine in Myelodysplastic Syndromes/Acute Myeloid Leukemia

Hypomethylating agents upregulate immune signaling in cancer through the viral defense pathway (Chiapinelli, 2015). Myeloid leukemia cell lines that were treated with the hypomethylating agent decitabine were shown to have an upregulation of PD-L1 expression (Yang, 2014). 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). Programmed death-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 (Yang, 2014). Programmed death ligand-1 (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.

1.5.4. Rationale for Durvalumab and Azacitidine Dosing Regimens

The dose of 75 mg/m^2 of subcutaneous azacitidine for 7 days is the established standard dose for higher-risk MDS and AML and is going to be used as control arm and for the combination with durvalumab as well.

The dose and schedule for durvalumab monotherapy (20 mg/kg every 4 weeks [Q4W]) was selected based on 2 sets of data: (1) the safety analysis of doses (0.1, 0.3, 1, 3, and 10 mg/kg once 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 > 40 µg/mL. This trough concentration is supported by 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. Pharmacokinetic simulations indicate that a similar overall exposure as represented by AUC (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 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is the recommended dose for the current study.

1.5.5. Rationale for the Study Design and Choice of Control Arm

Although historical data with azacitidine in higher-risk MDS and AML is available, these data have been generated in a population that varies from that proposed in this study due to the differences in the prognostic classification (shift in the MDS/AML definition from 30% to 20% blasts) risk classification (move from IPSS to IPSS-R in MDS) and response criteria have evolved over time.

This study will be conducted as a randomized Phase 2 study with two separate disease cohorts. The randomization will allow having a controlled study design with internal consistency being independent from historic control.

Both MDS and AML indications will be assessed in one study. Standard treatment with azacitidine will be the same for both cohorts. Potential study subjects will be assigned during screening to the MDS or AML cohort according to their percentage of blasts.

The selection of higher-risk MDS is based on the IPSS-R. Subjects with IPSS-R intermediate risk in combination with > 10% bone marrow blasts, poor or very poor cytogenetics are also eligible as these risk factors have poor survival rates of less than 1.5 years (Greenberg, 2012).

Both MDS and AML will be analyzed in separate cohorts as assessment of MDS and AML has evolved differently with specific response assessment guidelines and specific inclusion criteria. In addition, there is a major difference in the outcome for MDS and AML which makes separate analysis for MDS and AML required.

Azacitidine is approved globally and is the standard of care for higher-risk MDS. A positive opinion by the EMA CHMP for the treatment of elderly AML was obtained in September 2015 and in October 2015 the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has approved an expanded indication for the treatment of adult subjects aged 65 years or older with AML who are not eligible for HSCT. The expanded

indication now covers subjects who have > 30% myeloblasts according to the WHO classification; previously, the indication covered AML subjects with ≤ 30% blasts.

The primary endpoint ORR was chosen to allow early assessment of activity of the combination treatment in comparison to standard treatment. Time-to-event data (OS, PFS and other) will be analyzed as secondary endpoints for this Phase 2 trial.

The interim analysis on futility will support early assessment of efficacy and may minimize the number subjects exposed to the investigational regimen in the absence of signs of efficacy.

The combination of azacitidine and durvalumab is currently being evaluated in other studies. Currently there is no evidence for drug interactions in terms of dosing or overlapping toxicity. The combination of azacitidine with other PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab) are under clinical investigation.

The azacitidine dosing schedule for MDS and AML is identical (as per the EU approved dosing regimen). Due to the similar nature of MDS and AML in terms of toxicity, dose regimens will be identical in both disease cohorts.

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to evaluate the efficacy of subcutaneous azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population.
Secondary Objectives
The secondary objectives are to: • Assess the safety and tolerability of subcutaneous azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population • Assess the pharmacokinetics (PK) of durvalumab when given in combination with subcutaneous azacitidine in the defined study population.
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[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description
MDS Cohort		
Primary	Overall response rate	Overall Response Rate (ORR), (ie, CR, mCR, PR, HI) based on IWG 2006 response criteria (Appendix D).
Secondary	Time to response	Time from randomization to first documented response according to IWG 2006 response criteria (Appendix D).
Secondary	Relapse-free survival	Time from the date CR, PR or mCR is first documented until the date of documented relapse, death from any cause, or lost to follow-up, whichever occurs first according to IWG 2006 response criteria (Appendix D).

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Secondary	Cytogenetic response	Proportion of subjects achieving complete cytogenetic response or partial cytogenetic response according to IWG 2006 response criteria (Appendix D).
Secondary	Progression-free survival (PFS)	Time from randomization to the first documented PD or death due to any cause, whichever occurs first.
Secondary	Duration of response	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 IWG 2006 response criteria (Appendix D)
Secondary	Time to AML transformation	Time from randomization to AML transformation.
Secondary	Transformation to AML	Proportion of subjects with disease transformation to AML.
AML Cohort		
Primary	Overall response rate	Proportion of AML subjects achieving an overall response (CR or CRi) based on modified IWG 2003 response criteria for AML (Appendix K).
Secondary	Time to response	Time from randomization to first documented response based on modified IWG 2003 response criteria for AML (Appendix K).
Secondary	Relapse-free survival	Relapse-free survival is defined only for subjects who achieve CR or CRi and is measured as the interval from the date of first documented CR or CRi to the date of documented relapse, death from any cause, or lost to follow-up, whichever occurs first (Appendix K).
Secondary	Complete cytogenetic response (CyCR)	Proportion of subjects with complete cytogenetic response (CyCR) based on modified IWG 2003 response criteria for AML (Appendix K).
Secondary	Hematologic Improvement Rate	Rate of HI-NE + HI-P + HI-E according to IWG 2006 response criteria (Appendix D).
Secondary	Duration of response	Duration of response is defined as the time from the first documented CR/CRi to documented morphologic relapse, PD based on modified IWG 2003 response criteria for AML (Appendix K), or death due to any cause, whichever occurs first.
Phase 2: Both Cohorts		
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs), and relationship of AEs to study treatment, clinical laboratory evaluations.

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Secondary	Overall survival	Time from randomization to death due to any cause.
Secondary	One-year survival	The probability of survival at 1 year from randomization.
Secondary	PK parameters	Typical serum/plasma PK parameters for durvalumab, such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (Vz/F).
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AML = acute myeloid leukemia; CR = complete remission; HI = hematological improvement; HI-E = hematological improvement – erythroid response; HI-NE = hematological improvement – neutrophil response; HI-p = hematological improvement – platelet response; IWG = International Working Group; mCR = marrow complete remission; PD = progressive disease; CCI ; PK = pharmacokinetics.

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a Phase 2, multicenter, randomized, parallel-group, open-label study consisting of 3 phases: Screening, Treatment, and Follow-up.

To confirm the safety, ie, the absence of overlapping toxicities of the combination treatment regimen, an early safety monitoring will be performed based on approximately the first 12 subjects randomized. Details are provided in Section 3.2.2.2.

Approximately 72 subjects will be included in the MDS cohort and approximately 110 subjects in the AML cohort.

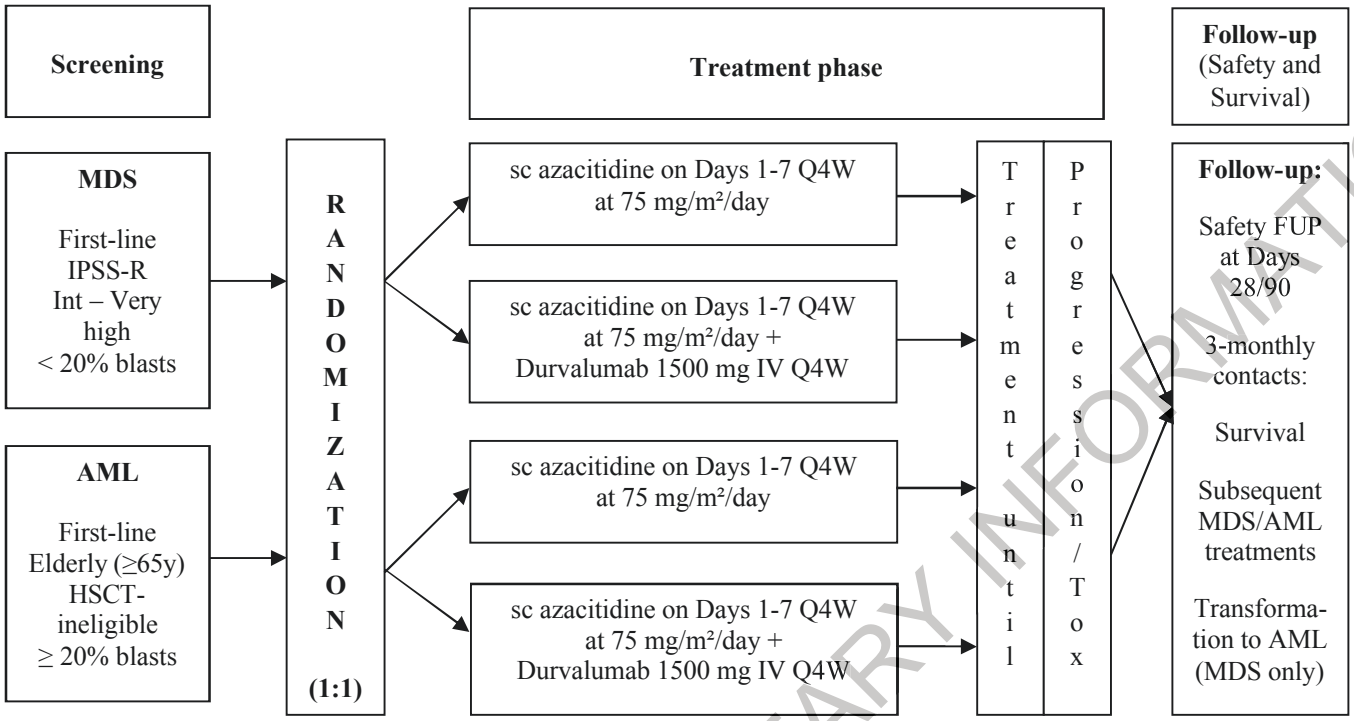
The enrollment period for this study is expected to last approximately 15 months. The treatment and follow-up periods are expected to conclude approximately 12 months after the last subject is randomized. Therefore, the total duration of the study is expected to be approximately 27 months, from first subject enrolled until the last subject last visit.

Eligible subjects will be randomized to receive subcutaneous azacitidine alone or in combination with durvalumab. The treatment phase will be conducted in 2 stages, with an interim analysis for futility purpose, for each of the 2 study cohorts as outlined in Section 9. The primary analysis will follow completion of Stage 2 with additional analyses conducted approximately 12 months after the last subject is enrolled, as described in Section 9.

Pharmacokinetic CCI [redacted] sampling will be performed in subjects receiving the combination therapy to assess durvalumab PK profile CCI [redacted].

Details regarding the PK CCI [redacted] sampling procedure are provided in Section 6.9 CCI [redacted]

Figure 1: Overall Study Design



AML = acute myeloid leukemia; FUP = follow up; HSCT = Hematopoietic Stem Cell Transplant; Int = intermediate; IPSS-R = Revised International Prognostic Scoring System; IV = intravenous; MDS = myelodysplastic syndromes; Q4W = every 4 weeks; sc = subcutaneous; Tox = toxicity.

3.2. Study Duration for Subjects

3.2.1. Screening Phase

Screening procedures are to be conducted within 35 days prior to randomization to ensure that all inclusion and exclusion criteria are satisfied. All study-specific screening procedures can only be performed after the subjects and the Investigators have signed the informed consent form (ICF).

During screening, a bone marrow biopsy and an aspirate, peripheral blood smears, blood samples and relevant clinical documentation will be obtained and will be sent for centralized review by an independent pathologist/cytogeneticist to ensure consistency in determination of diagnosis and baseline disease characteristics.

The diagnosis will be done according to the WHO classification for MDS and AML (Appendix B and Appendix I, respectively), IPSS-R for MDS (Appendix H), and the risk classification and cytogenetic risk category as per NCCN guidelines for AML subjects (Appendix J).

The results from central review must be available prior to the randomization to ensure proper stratification and proper cohort allocation.

On a case-by-case basis and after consultation with the medical monitor, it will be determined if local pathology reports can be used to support AML subjects' eligibility. Acute Myeloid

Leukemia subjects in the need of an urgent treatment start, may be randomized based on local pathology and cytogenetic results. Please note that a biopsy and an aspirate are still required prior to randomization for central review, CCI and final diagnosis confirmation. Sponsor's medical monitor will review specific eligibility criteria for all screened subjects prior to randomization of subjects via the IRT.

Details on the timing and quantity of material required will be specified in the laboratory manual for the study.

For all subjects, all transfusion records for the 56 days immediately preceding randomization should be collected whenever possible. Transfusion data should include the blood product transfused, number of units, reason for transfusion, and date of transfusion. Platelet transfusion data should include the platelet value for which the transfusion was deemed necessary and RBC transfusion data should include the hemoglobin (Hgb) value for which the transfusion was administered, if available.

Screening assessments and procedures are described in Section 6.1.

3.2.2. Treatment Phase

The study will be conducted in 2 stages. Eligible subjects will be randomized 1:1 to one of two treatment arms:

Treatment Arm A: Subcutaneous azacitidine (75 mg/m2 for 7 days Q4W) in combination with IV durvalumab at a dose of 1500 mg on Day1 Q4W

or

Treatment Arm B: Subcutaneous azacitidine alone at the dose of 75 mg/m2 for 7 days Q4W.

The randomization process will aim to balance prognostic factors between study arms. For both cohorts (MDS and AML) subjects will be randomized and stratified according to their cytogenetic risk:

- Intermediate risk versus poor risk for AML (see Appendix J),
- Very good, good and intermediate risk versus poor and very poor risk for MDS (see Appendix H, IPSS-R Cytogenetic Risk Groups).

The subject should begin treatment on the day of randomization via integrated response technology (IRT) 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.

On Day 1 of each 28-day treatment cycle, subjects will receive IV infusion of durvalumab prior to receiving the first dose of subcutaneous azacitidine. Azacitidine dosing should not begin until any immediate toxicities from durvalumab infusion have resolved.

Azacitidine dose and schedule may be adjusted as described in Section 7.2.2.1 for the management of unacceptable toxicity.

Interruption or delay of treatment with subcutaneous azacitidine for up to 42 days is permitted as outlined in Section 7.2.2.1 to enable recovery from investigational product (IP)-related toxicity. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the sponsor's

medical monitor must be consulted. When the start of a new treatment cycle with subcutaneous azacitidine is delayed for any reason, the infusion of durvalumab will also be delayed (in subjects randomized to the combination treatment arm), such that durvalumab and azacitidine continue 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 sponsor's medical monitor, the subject is experiencing clinical benefit.

For toxicity that is thought to be related to treatment with durvalumab, including immune-mediated adverse events (imAEs) or infusion-type reactions, as well as for nonimmune mediated reactions, the infusion of durvalumab may be slowed or interrupted, or a dose may be withheld, as described in Section 7.2.2.2. Dose reduction of durvalumab is not permitted.

In the event that a subject assigned to the combination treatment arm discontinues treatment with durvalumab or subcutaneous azacitidine because of drug-related toxicity, treatment with subcutaneous azacitidine or durvalumab monotherapy may continue until a discontinuation criterion is met (see Section 11.1). These subjects will be included in the ITT, safety and EE populations if they meet the respective criteria.

3.2.2.1. Scheduled Assessments

All screening/baseline assessments and procedures must be performed prior to randomization.

Safety assessments will include: physical examination with vital signs including body weight, ECOG performance status, and evaluation for AEs, laboratory evaluations, blood chemistries including lipase/amylase and thyroid function, complete blood cell count (CBC), pregnancy testing, coagulation tests, electrocardiogram (ECG), CCI pharmacokinetics and urinalysis.

Efficacy assessments will include bone marrow aspiration and biopsy, CBC with differential, cytogenetics, and transfusion records.

For more details on the evaluations and schedule, refer to the Table of events (Section 5).

3.2.2.2. Early Safety Monitoring Assessment

Azacitidine and durvalumab are generally well tolerated without anticipated overlapping toxicities. Azacitidine is related to well described gastrointestinal and hematologic AEs, mainly in the form of cytopenias. Durvalumab has a low frequency of immune-mediated adverse events similar to other immune checkpoint agents (See Section 1.4).

Safety of the combination therapy of durvalumab and azacitidine in MDS is currently also assessed in study MedImmune D4190C00007. The combination of oral azacitidine (CC-486) and durvalumab is currently also assessed in study CC-486-MDS-006.

Internal Celgene safety monitoring (safety review) will evaluate all available safety data and will assess on an ongoing basis the safety profile of the combination. External reviewers may be consulted if needed.

Early safety monitoring and a comparative safety evaluation will be performed on approximately the first 12 subjects randomized to the study (in order to analyze at least 6 subjects in the

combination arms). Safety will be evaluated on a real time basis through the electronic case report forms (eCRFs).

All available subject data, as well as information from study D4190C00007 as available, will be taken into account for the comparative safety evaluation.

If no major toxicity (eg unacceptable and/or unmanageable toxicities) is observed in the subjects randomized to the combination arm enrollment will continue without hold.

As enrollment continues, the first safety monitoring meeting will take place after the first 6 subjects are enrolled and the first three subjects randomized to combination treatment have completed two cycles of treatment.

At the first safety monitoring meeting, if major toxicity is observed in the first three subjects on combination therapy that is not observed in the azacitidine monotherapy arm, the safety review may conclude:

- To continue the randomization and perform a second safety review (see below) based on the next 6 subjects (3 additional subjects who have completed two cycles of combination treatment) as planned.
- To continue the randomization and perform a second safety review (see below) based on the next 6 subjects (3 additional subjects who have completed two cycles of combination treatment) and place enrollment on hold until these subjects have been observed for at least two cycles of combination treatment and have been reviewed by the second safety review meeting.
- To place enrollment on hold and amend or terminate the study
- To amend the protocol to place treatment randomization to the durvalumab combination arms on hold, but allow enrollment and assignment of subjects to the azacitidine monotherapy arms.

A second safety monitoring meeting will take place after approximately 12 subjects are enrolled and the first 6 subjects randomized to combination treatment have completed two cycles of treatment.

If no major toxicity has been observed in the subjects randomized to the combination arm that is not observed in the azacitidine monotherapy arm, the enrollment of the remaining subjects will continue.

If major toxicity is observed, the safety review may conclude:

- To continue the randomization with the early safety monitoring for additional subjects
- To place enrollment on hold and plan for an additional safety review meeting based on additional data from ongoing subjects
- To place enrollment on hold and amend or terminate the study.

3.2.2.3. Efficacy Parameters

Subjects' disease status will be assessed based on available clinical and laboratory assessments at the end of Cycles 3, 6 (ie, prior to Day 1 procedures of Cycles 4, 7) and at the end of every 3rd treatment cycle thereafter.

Because a hematologic response to treatment with subcutaneous azacitidine and/or durvalumab may be delayed, subjects will continue on treatment through 6 cycles. Subjects who satisfy one of the continuation criteria listed below may continue on to Cycle 7 and beyond.

Continuation criteria for MDS cohort:

- Overall response to treatment: CR, mCR, PR as per the International Working Group (IWG) criteria for MDS (Cheson, 2006), or
- Red blood cell (RBC) transfusion-independence for at least 56 consecutive days, or
- Any hematologic improvement (HI) as per the International Working Group (IWG) criteria for MDS (Cheson, 2006), or
- Any other clinical benefit, including no evidence of progressive disease.

Continuation criteria for AML cohort:

- Overall response to treatment: CR or CRi per modified IWG response criteria for AML (Cheson, 2003), or
- Any other clinical benefit including no evidence of progressive disease.

Confirmation of a RBC-transfusion-independent response/erythroid response (HI-E; see Appendix D) 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, and in respective eCRF. This will be compared to the subject's RBC transfusion history over the 56 days prior to randomization, as recorded in the appropriate eCRF during screening. The same will apply with regards to platelet transfusions.

Bone marrow samples (aspirate and/or biopsy), along with a peripheral blood smear and biological results will be submitted for review to an independent pathologist/cytogeneticist to provide consistency for determination of disease classification and response assessment.

Hematologic parameters including hemoglobin, WBC count, differential, and platelets will be assessed by the central laboratory at the frequency described in Section 5 (Table of Events).

Subjects who fail to meet one of the above criteria at the end of Cycle 6 and at the end of every 3rd treatment cycle thereafter will be discontinued from protocol-prescribed therapy and enter the Follow-up Phase.

A subject is considered evaluable for response if they have undergone the disease status assessment following treatment Cycle 6. A subject who discontinues from the treatment phase before the first postbaseline efficacy assessment (following treatment Cycle 3) will be replaced unless the subject had a documented progression of their disease or died from their disease or died from an IP-related event. An additional subject will be included in that cohort (MDS or

AML cohort). If one postbaseline disease assessment is performed, this assessment would be considered for response.

3.2.2.4. Pharmacokinetics [redacted] Assessment

All subjects receiving the combination treatment will participate in PK sampling procedures as described in Section 6.9. [redacted]

3.2.2.5. Discontinuation from Study Treatment

Prior to discontinuing treatment for a subject, it is recommended that the Investigator contact the sponsor's 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 a Treatment Discontinuation Visit within 7 days (Section 6.14) after 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 has been performed within 7 days of the Treatment Discontinuation Visit, it does not need to be repeated.

For all subjects, the reason for discontinuing treatment will be recorded in the eCRF and in the source document.

3.2.3. Follow-up Phase

3.2.3.1. Safety Follow-up Visit(s)

3.2.3.1.1. Safety Follow-up in Subjects Receiving Subcutaneous Azacitidine Alone

All subjects who receive at least one dose of subcutaneous azacitidine and discontinue treatment for any reason will be followed for at least 28 days after their last dose of subcutaneous azacitidine or after the Treatment Discontinuation Visit, whichever is later, for the assessment of safety-related parameters (see Section 6.15). After the 28-day period, any transformation to AML (for MDS subjects) and all SAEs made known to the Investigator that are suspected of being related to treatment with subcutaneous azacitidine must be reported.

A 28-day follow-up visit will be conducted 28 days following the last dose of subcutaneous azacitidine or during the Treatment Discontinuation Visit (whichever date is later) for assessment of the following parameters:

- Survival,
- Adverse events including AESIs,
- Physical examination (including vital signs, body weight, ECOG performance status),
- Laboratory parameters (hematology, serum biochemistry)
- Thyroid function tests,

- Urinalysis,
- Pregnancy test for females of childbearing potential (FCBP) only,
- Concomitant medications, therapies, and procedures,
- Red blood cell and platelet transfusions,
- Subsequent MDS/AML therapies,
- Disease transformation to AML (for MDS subjects only),
- CCI [redacted]

3.2.3.1.2. Safety Follow-up in Subjects Receiving Durvalumab/Subcutaneous Azacitidine Combination Therapy

All subjects who receive at least 1 dose of durvalumab 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 6.15). After the 28-day period for subcutaneous azacitidine and the 90-day period for durvalumab, any transformation to AML (for MDS subjects) and all SAEs made known to the Investigator that are suspected of being related to IP must be reported.

Subjects are to return to the study site 28 days after the last dose of subcutaneous azacitidine and 90 days after the last dose of durvalumab for assessment of the following parameters:

- Survival,
- Adverse events including AESIs (monitored until 28 days after last dose of subcutaneous azacitidine and 90 days after last dose of durvalumab),
- Physical examination (including vital signs, body weight, ECOG performance status),
- Laboratory parameters (hematology, serum biochemistry),
- Thyroid function tests,
- Urinalysis,
- Pregnancy test for FCBP only,
- Concomitant medications, therapies, and procedures (monitored until 90 days after last dose of durvalumab),
- CCI [redacted]
- Pharmacokinetics,
- Red blood cell and platelet transfusions,
- Subsequent MDS/AML therapies,
- Disease transformation to AML (for MDS subjects only),
- CCI [redacted]

3.2.3.2. Survival Follow-up

After completing the Safety Follow-up Visit(s), subjects will be followed and contacted every 3 months until death, lost to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to:

- Survival,
- Subsequent MDS/AML-related therapies,
- Disease transformation to AML (for MDS subjects only).

This follow-up will continue until the last active subject completes at least 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 be conducted every 3 months by telephone unless special circumstances exist (eg, the subject will visit the center for a nonstudy-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.

3.2.4. Discontinuation from Study

The following events are considered sufficient reasons for study discontinuation:

- Withdrawal of consent
- Death
- Lost to follow-up
- Study closure
- Screen failure
- Other (to be specified on the eCRF).

Subjects not meeting one of these criteria will still be part of the survival follow-up.

3.3. End of Trial

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

The study is expected to close when the last subject completes at least 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 subcutaneous azacitidine and/or durvalumab, without unacceptable toxicities and who have met criteria for treatment continuation may continue to receive subcutaneous azacitidine plus durvalumab or azaciticine alone provided by the sponsor through an extension to this protocol. (See Appendix O).

Subjects still on treatment at the end of trial who are not entering the extension phase will complete the End of Treatment and End of Study procedures and the appropriate eCRF forms for each. This should include the 28-day safety follow-up visit (and 90-day follow-up safety visit for patients on durvalumab). Subjects who have ended treatment prior to the End of Trial but are still active in the follow-up phase should be discontinued.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 182 eligible and evaluable subjects will be included in this study.

Eligible subjects for the study will require a documented diagnosis of either AML or MDS as defined in Section 4, and will be assigned to either the AML or MDS cohort based on the central laboratory diagnosis confirmation. Approximately 72 subjects will be included in the MDS cohort and approximately 110 subjects in the AML cohort.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

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

For both cohorts:

1. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
2. Have an ECOG performance status of 0, 1, or 2 (Appendix E).
3. Female subjects of childbearing potential[1] may participate, providing they meet the following conditions:
    a. Have 2 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 a highly effective method 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.

[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 in 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.

d. Refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.

4. Male subject must:
   a. Either practice true abstinence[3] 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 childbearing 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.
5. Understand and voluntarily sign a biomarker-specific component of the informed consent form prior to any study-related procedures conducted.
6. Willing and able to adhere to the study visit schedule and other protocol requirements.

MDS Cohort:

7. Age ≥ 18 years at the time of signing the informed consent form.
8. Central confirmation of diagnosis of previously untreated primary or secondary MDS as per WHO classification (Appendix B). Results of central pathology review are required prior to receiving the first dose of IP.
9. Central confirmation of the categorization of the MDS risk classification, as per the IPSS-R Intermediate risk with >10% blasts or poor or very poor cytogenetics, or IPSS-R High or Very High risk (Appendix H) (Results of central pathology review required prior to receiving the first dose of IP).

AML Cohort:

10. Age ≥ 65 years at the time of signing the informed consent form (ICF).
11. Central confirmation of diagnosis of one of the following untreated AML as per WHO classification (Appendix I):
    - Newly diagnosed, histologically confirmed de novo AML (bone marrow blasts ≥ 20%), or
    - AML secondary to prior MDS, or
    - AML secondary to exposure to potentially leukemogenic therapies or agents (eg, radiation therapy, alkylating agents, topoisomerase II inhibitors) with the primary malignancy in remission for at least 2 years.
12. Central confirmation of intermediate or poor risk status, based on Cytogenetics for Acute Myeloid Leukemia (Appendix J).

[3] 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.

4.2.2. Exclusion Criteria

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

For both cohorts:

1. Prior hematopoietic stem cell transplant.
2. Considered eligible for hematopoietic stem cell transplant (allogeneic or autologous) at the time of signing the ICF.
3. Prior exposure to azacitidine, decitabine or prior exposure to the investigational oral formulation of decitabine, or other oral azacitidine derivative.
4. Inaspirable bone marrow.
5. Use of any of the following within 28 days prior to the first dose of IP:
   - Thrombopoiesis-stimulating agents (eg, romiplostim, eltrombopag, Interleukin-11)
   - Any hematopoietic growth factors (ESAs, Granulocyte colony-stimulating factor (G-CSF) and other RBC hematopoietic growth factors (eg, Interleukin-3)
   - Any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment
6. Prior history of malignancies, (except MDS for AML subjects), unless the subject has been free of the disease for ≥ 2 years. However, subjects with the following history/concurrent conditions are allowed:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma in situ of the cervix
   - Carcinoma in situ of the breast
   - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system).
7. Pregnant or breast-feeding females or females who intend to become pregnant during study participation.
8. Subject has 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 [exclude only if active within the last 6 months prior to signing the ICF], 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:
   - Subjects with vitiligo or alopecia;
   - Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement for ≥ 3 months prior to signing the ICF; or

- Subjects with psoriasis not requiring systemic treatment

9. Significant active cardiac disease within the previous 6 months prior to signing the ICF, including:
   - New York Heart Association (NYHA) Class III or IV congestive heart failure (see Appendix F);
   - Unstable angina or angina requiring surgical or medical intervention; and/or
   - Significant cardiac arrhythmia
   - Myocardial infarction
10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment), uncontrolled hypertension, cardiac arrhythmia, pneumonitis, interstitial lung disease, active peptic ulcer disease or gastritis that would limit compliance with study requirement.
11. Known Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) infection, or evidence of active Hepatitis B Virus (HBV) infection.
12. Known or suspected hypersensitivity to azacitidine, mannitol, or durvalumab, its constituents, or to any other humanized monoclonal antibody.
13. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
14. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
15. Prior anti-CTLA-4, PD-1, or PD-L1 or other immune checkpoint mAb exposure.
16. Other investigational mAbs within 6 months prior to first dose of IP.
17. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of IP. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical, or local steroid injections (eg, intra-articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
18. History of primary immunodeficiency.
19. Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and for 30 days after the last dose of durvalumab).
20. Unwilling or unable to complete subject reported outcome assessments without assistance or with minimal assistance from trained site personnel and/or caregiver.

21. Subjects who have had clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS leukemia.
22. Presence of advanced malignant hepatic tumors.
23. Any of the following laboratory abnormalities:
    - Serum aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) > 2.5 × upper limit of normal (ULN)
    - Serum total bilirubin > 1.5 × 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
    - Serum creatinine > 2.5 × ULN.

MDS Cohort:

24. Any previous cytotoxic, cytostatic, hormonal, biological or immunological treatment for MDS (ESA with or without G-CSF are allowed under certain conditions, see exclusion criterion # 5).
25. Any investigational therapy within 28 days prior to the first dose of IP.
26. Use of hydroxyurea within 2 weeks prior to obtaining the screening hematology sample and prior to first dose of IP.
27. Absolute WBC count ≥ 15 × 10^9/L.

AML Cohort:

28. Previous cytotoxic, cytostatic, hormonal, biological or immunological treatment (ESA with or without G-CSF and iron chelating therapy and hydroxyurea are allowed under certain conditions, see exclusion criterion #5) or biologic treatment for AML.
29. Any investigational therapy within 28 days prior to the first dose of IP.
30. Use of hydroxyurea within 2 weeks prior to obtaining the screening hematology sample and prior to first dose of IP.
31. Prior use of targeted therapy agents (eg, FLT3 inhibitors, other kinase inhibitors).
32. Suspected or proven acute promyelocytic leukemia (FAB M3) based on morphology, immunophenotype, molecular assay, or karyotype; AML associated with t(9;22) karyotype, biphenotypic acute leukemia or AML with previous hematologic disorder such as chronic myelogenous leukemia or myeloproliferative neoplasms.
33. Acute myeloid leukemia associated with inv(16), t(8;21), t(16;16), t(15;17) karyotypes or molecular evidence of such translocations if not associated with a c-kit mutation.
34. Absolute WBC count ≥ 15 × 10^9/L (NOTE: Hydroxyurea is not allowed to attain a WBC count ≤ 15 x 10^9/L).
35. Known history or presence of Sweet Syndrome at screening

5. TABLE OF EVENTS

Table 3: Table of Events

Procedure/Assessment	Screening	Treatment Phase [a]						Follow-up Phase [b]	
	≤ 35 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 6		Cycles 7+	Treatment D/C [d]	Safety Follow-up Visit(s)[w]	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	×	--	--	--	--	--	--	--	--
IRT Registration	×	--	--	--	--	--	--	--	--
MDS or AML Diagnosis	×[e]	--	--	--	--	--	--	--	--
RBC and Platelet Transfusion History	×[f]	--	--	--	--	--	--	--	--
Demographics and Medical History	×	--	--	--	--	--	--	--	--
Prior Treatment for MDS /AML	×[g]	--	--	--	--	--	--	--	--
Prior General Medications and Procedures	×[h]	--	--	--	--	--	--	--	--
Examinations									
Physical Examination	×	×	--	×	--	×	×	×	--
Vital Signs[i]	×	×	×	×	×	×	×	×	--
Body Weight	×	×	--	×	--	×	×	×	--
Height	×	--	--	--	--	--	--	--	--
ECOG Performance Status	×	×	--	×	--	×	×	×	--
Electrocardiogram 12 Lead– Local	×[j]	--	--	--	--	--	×	--	--
Laboratory Assessments									
Urinalysis[k]	×	--	--	×	--	×	×	×	--

Table 3: Table of Events (Continued)

Procedure/Assessment	Screening	Treatment Phase [a]						Follow-up Phase [b]	
	≤ 35 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 6		Cycles 7+	Treatment D/C [d]	Safety Follow-up Visit(s) [w]	Additional Follow-up Contacts
		Day 1 [c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
Hematology [l]	×	×	×	×	×	Day 1 and Day 15	×	×	--
Coagulation Parameters [m]	×	--	--	--	--	--	--	--	--
Serum Chemistry including amylase/lipase [n]	×	×	×	×	x	Day 1 and Day 15	×	×	--
Thyroid Function [n]	×	×	--	×	--	×	×	×	--
Pregnancy Testing (FCBP only) [o]	×	×	--	×	--	×	×	×	--
Safety Assessments									
Assessing Adverse Events including AESIs	After signing ICF, until 28 days after the last dose of subcutaneous azacitidine (90 days after the last dose of durvalumab) or the Treatment Discontinuation Visit, whichever date is later								--
Monitoring for Transformation to AML (only for MDS subjects)	After signing ICF and until death, lost to follow-up, withdrawal of consent for further data collection, or end of trial								
Concomitant Medications, Therapies, and Procedures	From ICF signature until 28 days after the last dose of subcutaneous azacitidine (90 days after the last dose of durvalumab) or the Treatment Discontinuation Visit, whichever date is later								--
Disease Assessments									
Bone Marrow Aspirate and/or Biopsy [p]	×	--	--	End of every 3rd cycle Day 22 [p]			× [p]	--	--
Peripheral Blood Smear [p]	×	--	--	End of every 3rd cycle Day 22 [p]			× [p]	--	--
Cytogenetic Testing [p]	×	--	--	End of every 3rd cycle Day 22 [p]			× [p]	--	--
CCI **Pharmacokinetic Assessments**									
CCI [redacted]									
Bone marrow aspirate and/or biopsy sampling for cytogenetics, % plasma cells, CCI [redacted]	×	--	--	End of every 3rd cycle Day 22 [p]			× [p]	--	--

Table 3: Table of Events (Continued)

Procedure/Assessment	Screening	Treatment Phase [a]						Follow-up Phase [b]	
	≤ 35 Days Prior to C1D1	Cycles 1 – 2		Cycles 3 – 6		Cycles 7+	Treatment D/C [d]	Safety Follow-up Visit(s) [w]	Additional Follow-up Contacts
		Day 1 [c]	Days 8, 15, 22	Day 1	Day 15	Day 1			
CCI [redacted]									
Pharmacokinetics (subjects in combination treatment arm only) [r]	--	C1D1 (end of infusion), C2D1 (pre-dose)	--	C4D1 (pre dose and end of infusion) C6D1 (pre-dose)	--	--	--	×	--
IP Administration									
Subcutaneous Azacitidine Administration [s]	--	Day 1 to Day 7 of each 28-day treatment cycle					--	--	--
Durvalumab Administration 1-hour ± 5min (combination treatment arm only) [s]	--	Day 1 of each 28-day treatment cycle					--	--	--
IP Accountability	--	×	--	×	--	×	×	--	--
Response Assessments									
Blood Products Transfusion Assessment [t]	From Day -56 prior to randomization until 90 days after the last dose of IP or the Treatment Discontinuation Visit, whichever occurs later								--
IWG Response Assessment [u]	--	--	--	×	--	×	×	--	--
General Disease Status Assessment [v]	--	--	--	×	--	×	×	--	--

Table 3: Table of Events (Continued)

Procedure/Assessment	Screening	Treatment Phase [a]						Follow-up Phase [b]	
		Cycles 1 – 2		Cycles 3 – 6		Cycles 7+			
	≤ 35 Days Prior to C1D1	Day 1[c]	Days 8, 15, 22	Day 1	Day 15	Day 1	Treatment D/C [d]	Safety Follow-up Visit(s)[w]	Additional Follow-up Contacts
Subsequent MDS/AML Therapies	--	--	--	--	--	--	×	×	×
Survival	--	--	--	--	--	--	--	×	×
CCI [redacted]									

CCI [redacted]; AEs = adverse events; AESIs = adverse events of special interest; AML = acute myeloid leukemia; eCRF = electronic case report form; CxDx = Cycle x of Day x; D/C = discontinuation; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; FCBP = female of childbearing potential; Fe/TIBC = serum iron/serum total iron-binding capacity; ICF = informed consent form; IP = investigational product; IPSS(-R) = Revised International Prognostic Scoring System; IRT = Interactive Response Technology; IWG = International Working Group; MDS = myelodysplastic syndromes; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cell; WHO = World Health Organization.

a. The acceptable study visit window in the treatment phase is ±3 days for Cycles 1 through 6 and; ±7 days for Cycle 7 and beyond, unless otherwise noted for a particular assessment. 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 retreatment (see Section 7.2.3).

b. The study visit window for the 28-/90-day Safety Follow-Up Visit is ±3 days. If the visit is conducted prior to posttreatment Day 28 (Day 90 for durvalumab), the subject should be contacted on or after posttreatment Day 28 to obtain any new or updated information related to survival, AEs, concomitant medications, blood product transfusions, additional MDS/AML therapies, and/or disease transformation to AML (for MDS subjects). 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, lost to follow-up, withdrawal of consent to further contact or End of Trial (Section 6.1.5).

c. The first dose of IP in Cycle 1 should be administered on the day of entering the subject in the treatment phase via IRT, 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 eCRF and in the source document for all subjects, even if they never received IP. Reasons for discontinuation are provided in Section 11.1.

e. Documentation supporting MDS diagnosis (WHO classification - Appendix B), and IPSS-R risk classification (Appendix H) will be obtained during screening. Documentation supporting AML diagnosis (WHO classification - Appendix I) and cytogenetics risk classification (Appendix J) will be obtained during screening. Diagnosis and classification will be confirmed by the central laboratory. Results of central review are required prior to inclusion in the study. Bone marrow aspirate and biopsy samples, together with peripheral blood samples and clinical documentation, must be collected during screening, as detailed in Section 6.1.8. 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 randomization and will be recorded on the appropriate eCRF.
g. All prior treatments for MDS/AML, regardless of discontinuation date of treatment, must be recorded as detailed in Section 6.1.4.
h. All nonMDS/AML medications taken in the 4 weeks (28 days) prior to initiation of IP are to be collected on the appropriate eCRF.
i. Vital signs include measurements of blood pressure, pulse, body temperature and respiratory rate and body weight assessment as detailed in Section 6.1.5.2.
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 6.1.5.4.
k. Urinalysis is conducted at the central laboratory. Urine samples will be collected during screening, prior to administration of IP on Day 1 of every 3rd treatment cycle (ie, Cycle 3, 6, 9, etc), at the Treatment Discontinuation Visit and 28-day and 90-day Follow-Up Visits (see also Section 6.6.6.3).
l. Hematology includes a complete blood count with WBC differential and platelets as detailed in Section 6.6.6.1. 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, during treatment cycles, and at the Treatment Discontinuation and 28-day and 90-day Follow-Up Visits.
m. Coagulation parameters will be assessed during screening only. Retesting of coagulation parameters throughout the study can be performed if clinically indicated. Coagulation parameter assessment include: prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT) and fibrinogen.
n. Serum chemistry (to include amylase and lipase) and thyroid function parameters are detailed in Section 6.6.6.2. 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, during treatment cycles, and at the Treatment Discontinuation Visit and 28-day and 90-day Follow-Up Visits. Assessments do not need to be repeated at Cycle 1 Day 1 (C1D1) if screening assessments were performed within 7 days of C1D1.
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, at the Treatment Discontinuation Visit and 28-day and 90-day Safety Follow-Up visits (Section 6.6.7). The subject must 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 aspirate and/or biopsy and peripheral blood samples are required prior to beginning IP and during treatment on Cycle 3 Day 22, and Cycle 6 Day 22 or at the latest before starting Cycle 4 or 7. Subjects who continue beyond Cycle 6 will also undergo bone marrow examination every 3 treatment cycles on Day 22 or at the latest before starting the next cycle or when necessary to confirm suspected hematologic response or disease progression, and again upon treatment discontinuation (See Section 6.1.8, and 6.7.1). 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.

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r. Pharmacokinetic samples will be collected from all subjects receiving the combination treatment. Instructions for IP dosing and PK sample collection timepoints are provided in Section 6.9.
s. Investigational product (IP) administration should only start on Day 1 of each treatment cycle after all Day 1 procedures have been completed. For FCBP subjects, a negative pregnancy test performed within 72 hours prior to Day 1 IP administration must be documented. It is recommended that an antiemetic medication (eg, ondansetron) be taken 30 minutes prior to subcutaneous azacitidine administration during Cycle 1. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed. Durvalumab infusion will be monitored on each Day 1 of all cycles. Monitoring will consist of measuring vital signs 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) postinfusion, 60 minutes (± 5 minutes) postinfusion, followed by a 2-hour (± 15 minutes) period of observation.
t. The type of blood product transfused, number of units, reason for transfusion, date of transfusion, and hemoglobin and platelet values are to be collected beginning on C1D1, until 90 days after the last dose of IP or the Treatment Discontinuation Visit, whichever occurs later (see Section 6.7.6).
u. International Working Group Response Assessment based on IWG criteria for MDS (Appendix D) and modified IWG criteria for AML (Appendix K) is to be performed every 3 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 4, 7, 10, etc). See Section 6.7.3.

[v.] An assessment of disease status must be performed at the end of Cycle 6, based on available clinical and laboratory evaluations.
- Subjects who meet continuation criteria (Section 6.7.4) can continue on to Cycle 7 and beyond and disease status will be re-assessed every 3 cycles of treatment.
- Subjects who fail to meet continuation criteria at the end of Cycle 6 will be discontinued from protocol-prescribed therapy and enter the follow-up phase (Section 6.15).

[w.] Subjects will be followed for safety-related assessments for 28 days (90 days for durvalumab) posttreatment, or at the Treatment Discontinuation Visit, whichever is later.

6. PROCEDURES

All required study visits are described in the "Table of Events" above 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 Cycle 1 through Cycle 6 must be performed ± 3 days of the targeted day indicated in the table; all routine assessments of Cycles 7 and beyond must be performed ± 7 days of the targeted day; 28 day/90 day safety follow-up visits must be ± 3 days, posttreatment 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). The written informed consent form must be signed before any study-specific procedures are performed and any samples are collected for study-specific analysis. 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 receiving the first IP dose. Unless otherwise specified, screening assessments must take place, and eligible subjects receive their first dose of IP within 35 days after the date of the informed consent form 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.

Subjects who become screen failures can be rescreened once if it is reasonable to believe they will meet eligibility criteria during rescreening. If screening assessments are not within the allowed screening period, the rescreened subject must reconsent to participation in the study by signing a new and current informed consent form.

6.1.1. Myelodysplastic Syndromes/Acute Myeloid Leukemia Diagnosis, World Health Organization Classifications and Revised International Prognostic Scoring System (IPSS-R) Risk Classification

Screening procedures are conducted within 35 days prior to randomization to ensure that all inclusion and exclusion criteria are satisfied. All study-specific screening procedures can only be performed after the subject and the Investigator have signed the ICF.

During screening, a bone marrow biopsy and an aspirate, peripheral blood smears, blood samples and relevant clinical documentation will be obtained and will be sent for centralized review by an independent pathologist/cytogeneticist to ensure consistency in determination of diagnosis and baseline disease characteristics.

The central determination of the diagnosis will be done according to the WHO classification for MDS and AML (Appendix B and Appendix I respectively), IPSS-R (Appendix H), and risk

classification and cytogenetic risk category as per NCCN guidelines for AML subjects (Appendix J).

The results from central pathology review will have to be available prior to the randomization to ensure proper stratification and proper cohort allocation.

Details on the timing and quantity of material required will be specified in the laboratory manual for the study.

All hematology and bone marrow pathology reports generated by central laboratories and used to establish subjects' eligibility will be sent for sponsor review ahead of the planned randomization to allow for any deficiencies in documentation to be addressed. A checklist will be provided to the site to assist in compiling all necessary documentation during screening.

On a case-by-case basis and after consultation with the medical monitor, it will be determined if local pathology reports can be used to support AML subjects' eligibility. Acute Myeloid Leukemia subjects in the need of an urgent treatment start, may be randomized based on local pathology and cytogenetic results. Please note that a biopsy and an aspirate are still required prior to randomization for central review, CCI and final diagnosis confirmation. Celgene trial staff will review specific eligibility criteria for all screened subjects prior to randomization of subjects via the IRT.

Note: Any time subject-specific documentation is sent to the sponsor, all subject-identifying information must be redacted, and the subject's study-specific Identification 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 eCRF, as permitted by local regulations. Relevant medical history and current medical conditions, including MDS and AML signs and symptoms, must be recorded on the appropriate eCRF at screening.

6.1.3. Red Blood Cell and Platelet Transfusion History

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

Confirmation of a RBC-transfusion-independent response/erythroid response (HI-E; see Appendix D) requires that the Investigator documents the dates, numbers of units, reason for transfusion, and pretransfusion Hgb 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 prior to randomization, as recorded in the appropriate eCRFs during screening. The same will apply with regards to platelet transfusions.

6.1.4. Prior Medications, Procedures and Myelodysplastic Syndromes/Acute Myeloid Leukemia Treatments

All prior and current medications, including, prescription, over-the-counter, and herbal preparations taken for any indication from ICF signature will be recorded on the appropriate eCRF.

All prior treatments for MDS/AML as applicable will be recorded on the respective eCRF(s) regardless of dates of treatment.

Note: AML subjects with a past history of MDS are allowed to enter the study providing they meet all eligibility criteria. Please refer to Section 4.

6.1.5. Clinical Assessments

6.1.5.1. 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 eCRF.

6.1.5.2. Vital Signs, Body Weight and Height Measurements

The routine assessments described Section 6.6.3 must be present in the subject's source documentation and recorded on the appropriate eCRF.

Height is collected during screening only.

6.1.5.3. Eastern Cooperative Oncology Group Performance Status

Performance status at screening and interval time points will be assessed using ECOG criteria provided in Appendix E.

6.1.5.4. Electrocardiogram

Electrocardiograms (ECGs) performed during screening, at treatment discontinuation, and if clinically indicated during the course of the treatment part of the study, 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 and clinically significant finding(s) on the appropriate eCRF. 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.

6.1.6. Laboratory Assessments

Samples for blood hematology, serum biochemistry (including thyroid function and amylase/lipase), and urinalysis assessments will be sent to the central laboratory for analysis.

Refer to Section 6.6.6.1 for timing of required hematology assessments during the study.

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

6.1.6.1. Coagulation Parameters

Coagulation parameters will be assessed during screening. Re-testing of coagulation parameters throughout the study is only necessary if clinically indicated.

Coagulation parameter assessment include:

- Prothrombin time/international normalized ratio (PT/INR)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen.

6.1.7. Pregnancy Testing (Female of Child Bearing Potential Only)

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

- has not undergone a hysterectomy or bilateral oophorectomy, or
- 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 eCRF 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. An additional negative serum or urine (at Investigator's discretion) result must be verified by the Investigator prior to administration of IP (within 72 hours). Refer to Section 6.6.7 for details regarding pregnancy testing during the study and to inclusion criterion number 3 and 4 for contraception requirements of the protocol.

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

During screening, a bone marrow biopsy and an aspirate, peripheral blood smears, blood samples, and relevant clinical documentation will be obtained and will be sent for centralized review by an independent pathologist/cytogeneticist to ensure consistency in determination of diagnosis and baseline disease characteristics. CCI [redacted]

The central determination of the diagnosis will be done according to the WHO classification for MDS and AML (Appendix B and Appendix I respectively), IPSS-R (Appendix H), and risk classification and cytogenetic risk category as per NCCN guidelines for AML subjects (Appendix J).

The results from central review will have to be available prior to randomization to ensure proper stratification and proper cohort allocation.

For AML subjects in the need of an urgent treatment start, recent local pathology and cytogenetics reports may be considered for a review of subject eligibility. Please contact the medical monitor. This may be considered after the study screening procedures including bone

marrow biopsy and aspirate for central review, CCI and final confirmation have been conducted and the respective results are not yet available.

Details on the timing and quantity of material required will be specified in the laboratory manual for the study.

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 the informed consent form; this will enable resolution of any issues prior to subject's randomization. Therefore, the informed consent process and screening procedures (including bone marrow collection) should be planned with careful consideration for the 35-day screening period to avoid any potential need for rescreening due to exceeding the 35-day limit. Special handling requests such as return of materials to the site will be managed on an individual basis.

6.1.9. Cytogenetics

Bone marrow cytogenetic testing will be completed by the central laboratory. 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.

CCI [redacted]

6.2. Information to be Collected on Screen Failures

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

- Subject Number
- Informed consent date
- Demographics
- Screening Visit Date
- Reason subject did not qualify for the study

- All AEs / SAEs during the time period specified by the protocol
- Investigator's signature.

Any AEs 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 eCRF(s). Relevant information will also be recorded on a Screening Log. Subjects can be rescreened following discussion with the sponsor's medical monitor. All communications with sponsor's medical monitor will be documented.

6.3. Entering a Subject Into the Study

The written informed consent form must be signed by the subject and the Investigator 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 subject's randomization in the study. Randomization will occur via IRT to enable automated tracking and replenishment of IP. Specific contact information and instructions will be provided to each study site.

The IRT 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 randomization, 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. Such approvals must be documented.

Subjects included in the study will be randomly assigned to one of the two treatment arms, either subcutaneous azacitidine alone or in combination with durvalumab.

All subjects randomized to combination treatment will participate in PK sampling procedures. See Section 6.9 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. Durvalumab Infusion Monitoring

Subjects will be monitored during and after infusion of durvalumab. Vital signs will be measured as described in Section 7.2.1.3.

6.6. Safety

Safety assessments include:

- adverse events including AESIs,
- postinfusion 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 6.6.6.1)
- serum chemistry (to include amylase and lipase)
- Thyroid function tests (see Section 6.6.6.2)
- concomitant medications, therapies and procedures
- pregnancy testing (for FCBP subjects)
- urinalysis
- ECG
- coagulation parameters

6.6.1. Adverse Events

All subjects will be monitored for AEs including AESIs during the study. Refer to Section 10 for details regarding monitoring, recording, and reporting of AEs, including SAEs and AESIs.

Information about common side effects already known about azacitidine and durvalumab will be included in the subject informed consent form 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.

6.6.2. Transformation to Acute Myeloid Leukemia (only for Myelodysplastic Syndromes Cohort Subjects)

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

Events of disease transformation 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 eCRFs and in the subject's source documents. Documentation supporting the diagnosis of transformation to AML (eg, confirmatory

histology or cytology results, etc) must be provided at the time of reporting as an SAE. Refer to Section 10 for evaluation of AEs.

6.6.3. Physical Examination, Vital Signs and Weight

The following routine assessments are to be performed as specified below. Significant findings must be included on the appropriate eCRF and in the subject's source documents:

- Pulse
- Blood pressure (systolic and diastolic)
- Physical examination
- Body temperature
- Respiratory rate
- Body weight

The above assessments are to be performed during screening, on Day 1 of each cycle before administering the study IP, at the Treatment Discontinuation Visit, and at the 28day/90-day Safety Follow-Up Visits, as applicable. At every visit during treatment phase (Days 8, 15 and 22 for Cycles 1 and 2 and Days 1 and 15 for Cycle 3 onwards), vital signs that include blood pressure, pulse, body temperature and respiratory rate will be assessed.

6.6.4. 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 6.1.5.4.

6.6.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Appendix E) is to be assessed during screening, before IP dosing on Day 1 of each treatment cycle and at Treatment Discontinuation and 28-day/90-day Safety Follow-up Visits.

6.6.6. Hematology and Serum Chemistry Laboratory Evaluations

Hematology including coagulation parameters, serum chemistry including thyroid function and urinalyses samples will be processed as detailed in the study laboratory manual and sent to central laboratory for analyses and reporting, and are to be performed according to Section 6.6.6.1, Section 6.6.6.2, and Section 6.6.6.3. Any laboratory assessments described below may be repeated more frequently as clinically indicated and the results recorded in the appropriate eCRF and in the subject's source documents. 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) and corresponding normal range(s) should be recorded in the appropriate eCRF and in the subject's source documents.

Refer to Section 10.3 for guidance on the reporting of abnormal laboratory values and test results as AEs.

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

6.6.6.1. Hematology

Samples for hematology analyses will be collected prior to IP administration on Day 1 of each treatment cycle, whenever possible. The schedule of hematology assessments for subjects included in the study is as follows:

- During screening
- Cycles 1 and 2 – Days 1, 8, 15 and 22
- Cycles 3 and beyond – Days 1 and 15
- Treatment Discontinuation Visit
- 28-day Follow-up Visit (After discontinuation of subcutaneous azacitidine treatment)
- 90-day Follow-up Visit (Subjects who received durvalumab)

Complete blood count (CBC) for hematology assessment includes:

- Red blood cell count
- Hemoglobin
- Hematocrit
- Reticulocyte count
- Mean corpuscular volume (MCV)
- Red blood cell distribution width (RDW)
- Platelet count
- White blood cell (WBC) count with differential
  - Absolute neutrophils
  - Absolute lymphocytes
  - Absolute monocytes
  - Absolute eosinophils
  - Absolute basophils
  - Percent blasts

6.6.6.2. Biochemistry Parameters Including Thyroid Function

Samples for serum chemistry analysis will be collected prior to IP administration on Day 1 of each treatment cycle, whenever possible. Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing imAEs during

the conduct of this study. Potential imAEs may be similar to those seen with the use of other checkpoint inhibitors and may include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Hodi, 2010; Brahmer, 2012; Topalian, 2013). Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-mediated etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. Please refer to Appendix M for the management of imAEs.

The schedule of serum chemistry assessments for enrolled subjects is as follows:

- During screening
- Cycles 1 and 2 – Days 1, 8, 15 and 22
- Cycles 3 and beyond – Days 1 and 15
- Treatment Discontinuation Visit
- 28-day Follow-up Visit (After discontinuation of subcutaneous azacitidine treatment)
- 90-day Follow-up Visit (Subjects who received durvalumab)

Serum chemistry assessments include:

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

*The schedule of thyroid function testing is as follows:

- During screening
- Day 1 of each cycle
- Treatment Discontinuation Visit
- 28-day Follow-up Visit (After discontinuation of subcutaneous azacitidine treatment)
- 90-day Follow-up Visit (Subjects who received durvalumab)

6.6.6.3. Urinalysis

Urine samples should be obtained during screening and at the frequency specified below prior to IP administration as follows:

- During screening
- Day 1 of every 3rd cycle (eg, Cycles 3, 6, 9 etc)
- Treatment Discontinuation Visit
- 28-day Follow-up Visit (After discontinuation of subcutaneous azacitidine treatment)
- 90-day Follow-up Visit (Subjects who received durvalumab)

Urinalysis includes examination for glucose, ketones, blood, pH, and protein, and microscopic analysis if indicated.

6.6.7. Pregnancy Testing

For all female subjects of childbearing potential (FCBP – see Section 6.1.7), a screening serum pregnancy test is required.

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 the pregnancy test is negative.

Guidance for pregnancy testing during screening is provided in Section 6.1.7.

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

All prescription, over-the-counter, or herbal medications and therapeutic procedures received from the date of signature of ICF until 28 days after the last dose of subcutaneous azacitidine and 90 days after the last dose of durvalumab (or until the Treatment Discontinuation Visit, whichever period is longer) must be recorded on the appropriate eCRF page. Concomitant medications, therapies, and procedures are those that are received by the subject during their participation in the study as described above. 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 8 for details regarding concomitant medications and procedures.

6.7. Efficacy

6.7.1. Bone Marrow Aspirate, Biopsy and Peripheral Blood Smear

Samples will be processed as described in the Central Laboratory Manual and submitted for central review along with any pertinent clinical information. Determination of disease status as per the IWG 2006 criteria for MDS and IPSS-R for MDS or Modified IWG 2003 and

cytogenetic risk category as per NCCN guidelines for AML subjects will be done centrally. Results of central review will be utilized for determination of subjects' responses.

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

- At the end of every 3rd treatment cycle (before starting the next cycle, ideally on Day 22) to confirm suspected disease response or progression, and
- Upon treatment discontinuation.

This bone marrow sample, along with peripheral blood and blood smear slide(s) must be collected at the end of that cycle, but before Day 1 of the next cycle; early enough in order to allow sufficient time to obtain central laboratory results. Samples will be processed according to instructions provided in the Central Laboratory Manual and sent for:

- Central pathology review,
- Central laboratory assessments,
- Central cytogenetics review, and
- CCI [redacted]

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

- Response assessment,
- General disease status assessment, and
- Monitoring for transformation to AML (only for MDS cohort subjects).

Central laboratory results will be used to programmatically derive the subject's response.

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.

6.7.2. Cytogenetics

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

6.7.3. International Working Group Response Assessment

Hematologic response or improvement according to criteria from that of the International Working Group response criteria for MDS (Cheson 2006), and the modified International Working Group response criteria for AML (Cheson 2003) is to be assessed following every 3 treatment cycles prior to Day 1 procedures of subsequent cycles (ie, Cycles 4, 7, 10, etc) 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.

6.7.4. 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 may continue on to Cycle 7 and beyond, and will have disease status re-assessed prior to beginning each 3rd treatment cycle thereafter based on available clinical and laboratory evaluations and at Treatment Discontinuation Visit. Bone marrow and peripheral blood smear examinations will only be performed after Cycles 3, 6 and every 3rd cycle thereafter, unless additional bone marrow examination is deemed necessary by the Investigator.

For MDS subjects the continuation criteria are:

- Overall response to treatment: CR, mCR, PR as per the IWG criteria for MDS (Cheson, 2006), or
- Red blood cell transfusion-independence for at least 56 consecutive days, or
- Any HI as per the IWG criteria for MDS (Cheson, 2006) or
- Any other clinical benefit, including no evidence of progressive disease.

For AML subjects the continuation criteria are:

- Overall response to treatment: CR or CRi as per modified IWG response criteria for AML (Cheson 2003), or
- Any other clinical benefit, including no evidence of progressive disease.

Subjects who fail to meet one of the above 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 sponsor's 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/erythroid response (See Appendix D) requires that the Investigator documents the dates, numbers of units, reason for transfusion, and pretransfusion 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 prior to randomization, as recorded in the appropriate eCRFs during screening.

6.7.5. Hematology

Hematology results obtained from the central lab will be used to 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 6.6.6.1 for a list of hematology parameters being assessed by the central laboratory for this study.

6.7.6. Transfusion Assessment

The following will be recorded for all transfusions the subject received within 56 days (8 weeks) prior to randomization, until 90 days after the last dose of subcutaneous azacitidine or durvalumab or the Treatment Discontinuation Visit, whichever occurs later:

- Type of transfusion (eg, RBC 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.

Red blood cell 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.

Red blood cell transfusion-independent response or improvement will be assessed according to criteria from that of the IWG criteria for MDS (Cheson 2006) (Appendix D).

6.7.7. Survival, Transformation to Acute Myeloid Leukemia (only for Myelodysplastic Syndromes Cohort Subjects), and Subsequent Myelodysplastic Syndromes/Acute Myeloid Leukemia Therapies

All subjects discontinued from protocol-prescribed therapy for any reason should undergo treatment discontinuation procedures (Section 6.14) and be followed for survival, disease transformation to AML, and subsequent MDS/AML therapies (Section 6.15). Data regarding subsequent therapies, determination of disease progression, and date and cause of death will be recorded in the appropriate eCRF and in the subject's source documents.

[redacted]

6.9. Pharmacokinetics

All subjects receiving the combination therapy will participate in the PK procedures.

Durvalumab PK sample collection:

Blood samples for durvalumab PK analysis will be collected, processed, and analyzed. Samples will be collected at the following timepoints:

- Cycle 1 Day 1: end of infusion (EOI).
- Cycle 2 Day 1: preinfusion (-90 to -5 minutes prior to dose).
- Cycle 4 Day 1: preinfusion (-90 to -5 minutes prior to dose) and end of infusion.
- Cycle 6 Day 1: preinfusion (-90 to -5 minutes prior to dose).
- Safety Follow-up Visit (90 days after the last dose of durvalumab) .

[redacted]

CCI [redacted]

6.13. 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 eCRF. These evaluations should also appear in the subject's chart and/or other source documentation.

6.14. Discontinuation from Study Treatment

Prior to discontinuing a subject from study treatment, it is recommended that the Investigator contact the sponsor's 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 the Treatment Discontinuation Visit within 7 days of the treatment discontinuation, where the following procedures will be performed: including:

- AEs including AESI
- Physical examination
- Vital signs
- Body weight
- ECOG performance status
- Electrocardiogram
- Hematology
- Serum chemistry (to include amylase and lipase)
- Thyroid function tests
- Urinalysis
- Pregnancy test (FCBP only)
- Concomitant medications, therapies and procedures

- Transfusion assessment
- Bone marrow aspirate/biopsy and peripheral blood smear
- CCI [redacted]
- Cytogenetics
- IWG response assessment
- General disease status assessment
- CCI [redacted]
- CCI [redacted]
- Disease transformation to AML (MDS subjects only)
- Subsequent MDS/AML 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 on the eCRF and in source documents for all randomized subjects.

In the event that a subject assigned to the combination treatment arm discontinues treatment with durvalumab or subcutaneous azacitidine because of drug-related toxicity, treatment with single-agent durvalumab or subcutaneous azacitidine may continue until any discontinuation criterion is met.

6.15. 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 subcutaneous azacitidine and 90 days after the last dose of 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 subcutaneous azacitidine or 90 days after last dose of durvalumab)
- physical examination
- vital signs
- body weight
- ECOG performance status
- hematology
- serum chemistry (to include amylase and lipase)
- thyroid function tests
- pregnancy testing (FCBP only)

- urinalysis
- concomitant medications, therapies and procedures
- transfusion assessment
- subsequent MDS/AML therapies
- survival

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 Safety Follow-up Visit(s) until the last active subject reaches 12 months of treatment, unless additional follow-up is needed to evaluate time-to-event endpoints (eg, PFS and survival), or until death, lost to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to:

- survival
- subsequent MDS/AML therapies
- disease transformation to AML (only for MDS cohort subjects).

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).

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. Durvalumab

Durvalumab will be supplied by Celgene 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 durvalumab at a concentration of 50 mg/mL. Durvalumab is stored at 2°C to 8°C (36°F to 46°F) and must be used before the individually assigned expiry date on the label.

Site to supply the following:

- Intravenous 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 must not be infused through an IV line in which other solutions or medications are being administered.

Refer to the current durvalumab IB for detailed information about the physical properties of durvalumab and to the pharmacy manual for additional preparation, administration, or storage information.

7.1.2. Azacitidine

Azacitidine will be supplied by Celgene as a sterile lyophilized powder containing 100 mg of azacitidine and 100 mg of mannitol per vial. Each single-use vial will be supplied in single-count cartons.

Refer to the current azacitidine IB for detailed information about the physical properties of azacitidine and to the pharmacy manual for additional preparation, administration, or storage information.

7.2. Treatment Administration and Schedule

7.2.1. Treatment Administration

Subjects will receive treatment in 28-day cycles as described in the section below and may continue to receive the protocol therapy for as long as they benefit from the treatment or until treatment is discontinued for reasons detailed in Section 6.14.

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

7.2.1.1. Azacitidine Dispensation and Administration

Azacitidine will be administered on Days 1 to 7 of each treatment cycle. The subject may not receive IP for each treatment cycle until all Day 1 procedures have been completed.

Vials/syringes should be used for the specific subjects to whom they are assigned, and must not be shared between subjects.

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.

Subjects will receive azacitidine 75 mg/m^2/day subcutaneous for 7 days (Days 1 to 7) every 28 days. In the event 2 or fewer doses are missed during the 7-day dosing period, dosing should continue so the subject receives the full 7 days of therapy. If 3 or more days are missed during the 7-day dosing period, the Investigator should contact the sponsor and a decision on dosing will be made on a case-by-case basis.

Subjects assigned to the combination treatment arm will have azacitidine administered on Day 1 of each treatment cycle approximately one hour after completion of the durvalumab infusion, after resolution of any related AE immediately after durvalumab infusion, if any.

If the dose of azacitidine is modified during the course of the study (Section 7.2.2.1) and benefit is demonstrated at a dose lower than 75 mg/m^2, that dose should be maintained during subsequent cycles that are given (unless toxicity develops).

7.2.1.2. Durvalumab Dispensation and Administration

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. Durvalumab does not contain preservatives and any unused portion must be discarded.

Sites should follow standard and local aseptic procedures and instructions from the pharmacy manual 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.

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

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.

Subjects will receive durvalumab, 1500 mg intravenously on Day 1 of each 28-day treatment cycle by IV infusion over approximately 1 hour (± 5 minutes). Infusions of durvalumab may be interrupted, slowed, or discontinued in order to address toxicity, but dose reduction of durvalumab is not permitted (see Section 7.2.2.2).

Refer to the current durvalumab IB for detailed information about the physical properties of durvalumab and to the pharmacy manual for additional preparation, administration, or storage information.

7.2.1.3. Monitoring of Durvalumab 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, at the end of the durvalumab infusion (± 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion 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 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.

7.2.1.4. Missing Doses

Subjects will receive subcutaneous azacitidine 75 mg/m^2/day for 7 days every 28 days until the end of the study, unless they are discontinued from the treatment. In the event 2 or less doses are missed during the 7-day dosing period, dosing should continue so the subject receives the full 7 days of therapy. If 3 or more days are missed during the 7-day dosing period, the Investigator should contact the sponsor and a decision on dosing will be made on a case-by-case basis.

In order to optimally benefit from the azacitidine treatment, Investigators should aim to treat subjects for at least 6 cycles. However, subjects may be discontinued from the treatment per Investigator discretion, even during the first 6 cycles, for any of the reasons detailed in Section 11.1. If the dose of subcutaneous azacitidine is modified during the course of the study (Section 7.2.2.1) and benefit is demonstrated at a dose lower than 75 mg/m^2, that dose should be maintained during subsequent cycles that are given (unless toxicity develops). All subjects discontinued regardless of the reason will be followed for a period of 28 days following the date of the last dose of subcutaneous azacitidine or the date of the Treatment Discontinuation Visit (whichever date is later) for collection of AEs and will also be followed for survival until the end of the study.

7.2.2. Dose Modifications and Toxicity Management

7.2.2.1. Azacitidine

The first cycle of subcutaneous azacitidine should always be given at 100% of the dose, regardless of the subject's laboratory values (provided that the subject is allowed to enter the study based on the inclusion and exclusion criteria).

Subjects should be monitored for hematologic and renal toxicity; a delay in starting the next cycle or dose reduction as described by the guidance below may be necessary and followed at the investigator's discretion. Assessment to modify the dose should be made taking into consideration the subject's clinical condition including all adverse events (eg, bleeding or infections) and the subject's underlying disease status.

The Investigator should contact the sponsor's medical monitor for guidance on subcutaneous azacitidine dose modification, if needed.

Dose Modifications due to Nonhematological Toxicity

Following receipt of any dose of subcutaneous azacitidine, subsequent cycles may be delayed if a certain level of toxicity occurs after the previous dose. Any subject who experiences a nonhematological AE with Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) toxicity Grade 3 or 4 that is an escalation from his or her status at baseline (prior to the first dose) should have subcutaneous azacitidine temporarily discontinued until the toxicity grade returns to less than Grade 3. Subcutaneous azacitidine should be permanently discontinued if nonhematological toxicity persists at Grade 3 or 4 for more than 21 days, despite the temporary interruption of subcutaneous azacitidine.

Dose Modifications due to Hematological Toxicity

Treatment with subcutaneous azacitidine is associated with anemia, neutropenia, and thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as specified in Section 6.6.6.1 and as needed to monitor response and toxicity.

Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (ie, blood count at recovery ≥ Nadir Count + (0.5 × [Baseline count – Nadir count]).

Subjects without reduced baseline blood counts (ie, WBC ≥ 3.0 × 10^9/L and absolute neutrophil count [ANC] ≥ 1.5 × 10^9/L and platelets ≥ 75.0 × 10^9/L) prior to first treatment

If hematological toxicity is observed following subcutaneous azacitidine treatment, the next cycle of subcutaneous azacitidine therapy should be delayed until platelet count and ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to Table 4. Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of subcutaneous azacitidine dose adjustment in subjects without reduced baseline blood counts is provided in Appendix N2.

Table 4: Dose Modifications for Subcutaneous Azacitidine in Hematologic Toxicity

Nadir Counts		% Dose in the Next Cycle if recovery[a] is not achieved in next 14 days
ANC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

ANC = absolute neutrophil count
[a] Recovery = counts ≥ nadir count + (0.5 × [baseline count – nadir count]).

Subjects with reduced baseline blood counts (ie, WBC < 3.0 × 10^9/L or ANC < 1.5 × 10^9/L or platelets < 75.0 × 10^9/L) prior to treatment

Following subcutaneous azacitidine treatment, if the decrease in ANC or platelets from that prior to treatment is less than 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of subcutaneous azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is> 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to Table 5.

Table 5: Dose Modifications Based on Bone Marrow Cellularity

Bone Marrow Cellularity	% Dose in the Next Course if recovery[a] is not achieved in next 14 days	
	Recovery ≤ 21 days [a]	Recovery > 21 days [a]
15 – 50%	100%	50%
< 15%	100%	33%

[a] Recovery = counts ≥ nadir count + (0.5 × [baseline count – nadir count])

Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops). A flow diagram for the determination of subcutaneous azacitidine dose adjustment in subjects with reduced baseline blood counts is provided in Appendix N1.

Renal Dysfunction During Subcutaneous Azacitidine Therapy

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in subjects treated with intravenous azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L) developed in 5 subjects with chronic myelogenous leukemia (CML) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate

(< 20 mmol/L) occur, the dose should be reduced by 50% on the next cycle. Similarly, if unexplained elevations in serum creatinine or BUN to ≥ 2-fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops).

7.2.2.2. Durvalumab

Please refer to Appendix M for detailed instructions for dose modifications and toxicity management.

7.2.3. Retreatment Criteria

In order to proceed to the next cycle, subjects must continue to meet entry criteria regarding renal and hepatic function (AST/SGOT or ALT/SGPT ≤ 2.5 × ULN, serum total bilirubin ≤ 1.5 × ULN, serum creatinine ≤ 2.5 × ULN).

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 sponsor's 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 sponsor's medical monitor, the subject is experiencing clinical benefit. Justification of the subject continuing in the study must be recorded in the source documents. Subjects assigned to the combination treatment arm will have azacitidine administered on Day 1 of each treatment cycle approximately one hour after completion of the durvalumab infusion, after resolution of any related AE immediately after durvalumab infusion, if any.

Prior to discontinuing a subject from study treatment, it is recommended that the investigator contact the sponsor's 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.

7.2.4. Overdose

7.2.4.1. Definition of Overdose

Overdose, as defined for this protocol, refers to azacitidine and durvalumab dosing only.

On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of subcutaneous azacitidine or intravenous durvalumab assigned to a given subject, regardless of any associated AEs 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 subcutaneous azacitidine, any amount over the protocol-specified dose
- For IV durvalumab, 10% over the protocol-specified dose.

7.2.4.2. Actions Taken in the Event of an Overdose

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 10.1 for the reporting of AEs associated with overdose.

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptoms of overdose are not established.

An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.

An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of durvalumab occurs in the course of the study, then the Investigator or other site personnel will inform appropriate Celgene representatives immediately, or no later than 24 hours of when he or she becomes aware of it. The designated Celgene representative will work with the Investigator to ensure that all relevant information is provided to Celgene.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 10.5.

For other overdoses, reporting must occur within 30 days.

7.2.5. Discontinuation

Reasons for discontinuing a subject from the investigational product and/or from the study are listed in Sections 11.1 and 11.2.

Because a hematologic response to treatment with subcutaneous azacitidine 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 subject's eCRF and source documents.

7.3. Method of Treatment Assignment

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

Investigator or designated site staff will be assigned password protected, identification numbers that give them authorization to call into the IRT to enroll a subject. At screening, the Investigator or designated staff will call into the IRT and provide the requested identifying information for the subject. The IRT will then confirm the assignment of a unique subject number. If a subject is screened but not enrolled, the screen-failure must be registered using the IRT. During the

treatment phase, calls will be placed to the IRT 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 IRT are found in the IRT User Manual.

7.4. 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.

7.5. Investigational Product Accountability and Disposal

The Investigator(s) or designee is responsible for taking an inventory of each shipment of investigational product received and comparing it with the accompanying shipping order/packaging slip. The investigator(s) will verify the accuracy of the information on the shipping order/packaging slip and call IRT to register receipt at the site of the investigational product.

At the study site, investigational product will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of investigational product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any investigational product is lost or damaged or if the study subject misses a dose, this information should be documented in the study subject's eCRF and source documents.

Investigational product accountability will be assessed by the Investigator or designee. Applicable information such as lot number, vial count, and expiration date should be collected.

The investigator(s) or designee(s) is responsible for accounting for all IP during the course of the study according to applicable regulatory requirements. Any unused IP must be 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. 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 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).

7.6. Investigational Product Compliance

Subjects will receive azacitidine and durvalumab at the investigation site during the study. Administration of all IP will be recorded by the Investigator on the subject's eCRF, including dispensing, dosing, and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All prior and concomitant medications (prescription and nonprescription), treatments, and therapies taken from signing of the ICF up to 28 days after the last dose of subcutaneous azacitidine or up to 90 days after the last dose of for durvalumab, or up to the Treatment Discontinuation Visit, whichever date is later, must be recorded on the appropriate subject's eCRF.

All prior treatments for MDS, including ESAs, thrombopoiesis-stimulating agents (TSAs), iron-chelating agents, or other medications considered supportive care for MDS should be recorded on the respective subject's eCRF(s) regardless of the date of these treatments. All prior treatments for AML, as applicable, should also be recorded on the appropriate subject's eCRF(s).

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.

8.1. 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 granulocyte colony stimulating factor [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. Red blood cell and platelet transfusions will be considered concomitant procedures and should be collected on the appropriate subject's eCRF.

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 randomization. Initiation, modification, and/or discontinuation of iron-chelating agents during the treatment phase of the study is discouraged and should be discussed with the sponsor's 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. If nausea/vomiting is not significant, further antiemetic prophylaxis may not be needed. Pretreatment or posttreatment 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 subject's eCRF.

Treatment with antidiarrheal medications is recommended at the first sign of diarrhea. Premedication with antidiarrheal medication for subsequent doses of subcutaneous azacitidine

and/or durvalumab may be appropriate. Pre and posttreatment with an antidiarrheal must be recorded in the subject's eCRF 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 $< 0.5 \times 10^9$/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 subject's eCRF. 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 7.2.2 remain applicable. Discontinuation of secondary prophylaxis with myeloid growth factors should be considered by the Investigator as clinically appropriate.

Concurrent systemic corticosteroids for non-cancer-related conditions are allowed (eg, insulin for diabetes and hormone replacement therapy), provided the subject is on a stable or decreasing dose for ≥ 1 week prior to the first dose of IP, and provided the exclusion criteria #17 is met. Initiation, modification, and/or discontinuation of corticosteroids during the treatment phase of the study is discouraged and should be discussed with the sponsor's medical monitor first whenever possible.

For AML subjects, the use of hydroxyurea is permitted up to 2 weeks prior to the screening hematology sample and is prohibited during the whole study participation.

8.2. 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 IV injection, decitabine, or other demethylating agents
- Lenalidomide, thalidomide, and a proprietary series of drugs with immunomodulatory and other properties (IMiDs®)
- Erythropoiesis stimulating agents and other hematopoietic growth factors (eg, interleukin-3)
- Romiplostim and other TSAs (eg, interleukin-11, eltrombopag)
- Hydroxyurea for MDS subjects only (for AML subjects, see Section 8.1),
- 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 tumor necrosis factor – alpha (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 sponsor's medical monitor.
- Live attenuated vaccines during the study through 30 days after the last dose of durvalumab.

Refer to Section 4.2.2 for exclusion criteria pertaining to prohibited concomitant medications.

8.3. Required Concomitant Medications and Procedures

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

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2 randomized, multicenter, open-label, study evaluating the efficacy of subcutaneous azacitidine in combination with durvalumab in the defined study population (see Section 4).

The study will be run in two separate, parallel cohorts with separate inclusion and exclusion criteria as well as separate response criteria (MDS and AML).

Subjects in each cohort will be randomized into a monotherapy arm and a combination therapy arm with 1:1 allocation ratio using dynamic randomization method. At randomization, subjects will be stratified by cytogenetic risk (Intermediate risk versus poor risk for AML cohort, very good, good and intermediate risk versus poor and very poor risk for MDS Cohort). In each cohort, the study will be conducted in two stages, with an interim analysis for futility purposes following completion of the first stage and the primary analysis following completion of second stage. The interim analysis for futility will be performed independently in each cohort, and there will not be any recruitment hold between stages within each cohort.

The primary objective is to evaluate the efficacy of subcutaneous azacitidine in combination with durvalumab as compared with subcutaneous azacitidine alone in the defined study population (see Section 4). The secondary objectives are to assess the safety and tolerability of subcutaneous azacitidine in combination with durvalumab; to assess overall survival, and additional secondary efficacy criteria including but not limited to time to response, duration of response, cytogenetic responses, proportion of MDS subjects transforming to AML and time to AML transformation, and duration of remission in AML subjects; to evaluate the PK profile of durvalumab in combination with subcutaneous azacitidine; CCI [redacted]

This section defines the subject populations for the statistical data analyses, the justifications of sample sizes for each cohort, 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.

9.2. Study Population Definitions

For the purpose of statistical analyses and data presentation, the study populations are defined as follows.

9.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects. The primary efficacy analyses will be performed on the ITT population.

9.2.2. Efficacy Evaluable Population

The supportive efficacy analyses will be performed on the efficacy evaluable (EE) population, which will include all ITT subjects who completed 6 cycles of treatment, unless they have

established an earlier response or who discontinued the study due to death or disease progression.

Subjects who do not have an on-treatment disease assessment and discontinue due to death or disease progression without postbaseline response assessment will be considered as nonresponders.

9.2.3. Safety Population

The safety population will include all subjects who take at least 1 dose of IP.

9.2.4. Pharmacokinetic Population

The PK population includes all subjects who received at least one dose of study treatment and who have at least 1 measurable durvalumab concentration datum. For subjects who are determined to be noncompliant with respect to administration of durvalumab, or for subjects with incomplete data, a decision as to their inclusion in the population will be made on a case-by-case basis prior to the analysis.

9.3. Sample Size and Power Considerations

9.3.1. Myelodysplastic Cohort

Sekeres et al. (Sekeres, 2014) demonstrated that treating subjects with higher-risk MDS resulted in an ORR (CR, mCR, PR, HI) of 36% after four cycles of azacitidine monotherapy. This number is consistent with the "HI and better" rate from the AZA-MDS-001 trial of 36.4%. Assuming a treatment effect of 100% relative improvement of ORR (from 36% to 72% ORR), a sample size of 72 subjects will provide a power of 90% to detect such an effect at the 5% level of statistical significance.

An interim analysis for futility purpose will be conducted on the first 30 subjects who have completed 6 cycles of treatment unless they have established an earlier response (i.e. for arm A, 6 cycles of durvalumab and azacitidine, arm B, 6 cycles of azacitidine) or discontinued due to death or disease progression. The MDS cohort will be completed to include a total of 72 efficacy evaluable MDS subjects if one of the below conditions is met:

- If the overall response rate (considering the composite score of CR + PR + mCR + HI) in the combination arm is numerically higher than or equal to the control group (azacitidine alone) or,
- If the response rate of one of the components of this composite score (in particular CR rate) in the combination arm is numerically higher than or equal to the control group (azacitidine alone) or,
- If evidence of a clinical meaningful difference in favor of the combination arm in a secondary endpoint (eg, duration of response) is provided.

If none of these conditions is met, then the cohort might be terminated. The DMC will review the data at the time of interim analysis and will provide recommendation/advice to Celgene.

9.3.2. Acute Myeloid Leukemia Cohort

Dombret and Fenaux (Dombret, [2015]; Fenaux, [2010]) showed the response (CR + CRi) rate is 25% in AML subjects treated with azacitidine. Assuming a treatment effect of 100% relative improvement of CR (from 25% to 50% absolute CR rates), a sample size of 110 subjects will provide a power of 80% to detect such an effect at the 5% level of statistical significance.

An interim analysis for futility purpose will be conducted on the first 50 subjects who have completed 6 cycles of treatment unless they have established an earlier response (i.e. for arm A, 6 cycles of durvalumab and azacitidine, arm B, 6 cycles of azacitidine) or discontinued due to death or disease progression. The AML cohort will be completed to include a total of 110 efficacy evaluable AML subjects if one of the below conditions is met:

- If the overall response rate (considering the composite score of CR + CRi) in the combination arm is numerically higher than or equal to the control group (azacitidine alone) or,
- If the response rate of one of the components of this composite score (in particular CR rate) in the combination arm is numerically higher than or equal to the control group (azacitidine alone) or,
- If evidence of a clinical meaningful difference in favor of the combination arm in a secondary endpoint (eg, duration of response) is provided.

If none of these conditions are met, then the cohort might be terminated. The DMC will review the data at the time of interim analysis and will provide recommendation/advice to Celgene.

9.4. 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 (SOC) and preferred term (PT).

9.5. Subject Disposition

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

9.6. Efficacy Analysis

Primary efficacy analyses will be performed on the ITT population. Supportive efficacy analyses will also be performed using the EE population.

9.6.1. Primary Efficacy Analysis

9.6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be programmatically derived using the results/assessments generated by the central morphologic/cytogenetic and hematology laboratories. This analysis will be conducted after completion of the Stage 1 and Stage 2 portions of the study. A subject is considered evaluable for response if they have undergone the disease status assessment following treatment Cycle 6. Subjects who discontinue from the treatment phase before the first postbaseline efficacy assessment (following treatment Cycle 3) and will be replaced unless the subject had a documented progression of their disease or died will be considered as nonresponders. If one postbaseline disease assessment is performed, this assessment would be considered for response.

The primary efficacy analysis will be based on the ITT population. Analysis based on the EE population will be confirmative and supportive. Test statistics on the difference of proportion of overall response between monotherapy arm and combination therapy arm using unpooled estimate of variance will be used for the primary efficacy endpoint analysis along with confidence intervals.

9.6.1.1.1. Myelodysplastic Syndromes Cohort

For the MDS cohort, the primary efficacy endpoint is the overall response rate (defined as CR, PR, mCR and/or HI) as determined using the IWG 2006 response criteria for MDS. The ORR will be summarized together with 95% CI. Subjects discontinued before 6-cycle treatment without achieving overall response will be counted as nonresponders.

9.6.1.1.2. Acute Myeloid Leukemia Cohort

For AML cohort, the primary efficacy endpoint is the overall response rate (CR or CRi) based on modified IWG 2003 response criteria for AML. The ORR will be summarized together with 95% CI. Subjects discontinued before 6-cycle treatment without achieving overall response will be counted as nonresponders.

9.6.1.2. Secondary Efficacy Endpoints

Secondary endpoints are listed in Section 2.

Overall survival is defined as the time between randomization and death/censored date. Subjects who die, regardless of the cause of death, will be considered to have had an event. Subjects who are alive at the time of clinical data cut-off date will be censored at the last assessment date at which the subject was known to be alive. All subjects who were lost to follow-up prior to the clinical data cut-off date will also be censored at the time of last contact. The OS curve and OS at 12 months will be estimated using Kaplan-Meier (KM) method.

Rate of hematological improvement – erythroid response (HI-E), hematological improvement – platelet response (HI-P) and hematological improvement – neutrophil response (HI-N) according to IWG 2006 response criteria (Appendix D), will be assessed for AML subjects as secondary efficacy endpoint.

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 for MDS Cohort, CR or CRi for AML Cohort) is 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 the KM method.

Duration of response will be calculated only for subjects who achieve CR, mCR, PR or HI for the MDS Cohort, CR or CRi for the AML Cohort. Duration of response is defined as the time from first response observed until relapse or PD. Duration of response will be censored at the last date that the subject is known to be progression-free for:

1. subjects who have not progressed at the time of analysis;
2. subjects who have withdrawn consent or are lost to follow-up prior to documentation of progression.

Duration of response will be analyzed using the KM method. Median duration of response along with two-sided CI will be provided for each cohort.

Relapse-free survival is defined only for subjects who achieve CR, PR or mCR for MDS subjects, CR and CRi and for AML subjects, and is measured as the interval from the date of first documented response to the date of disease relapse, death from any cause, or lost to follow-up, whichever occurs first, censoring for subjects alive in continuous response. The RFS curve will be estimated using KM method.

External central pathology/cytogenetic reviewers will review the morphologic/cytogenetic data from bone marrow aspirate (BMA), bone marrow biopsies (if performed), and/or peripheral blood smears to determine whether a subject achieved a cytogenetic response (complete or partial cytogenetic responses for MDS subjects and cytogenetic complete response for AML subjects). For cytogenetic response evaluable subjects, the number and percentage of subjects who achieve the responses will be summarized.

MDS Cohort:

Progression-free survival is calculated as the time from randomization to the first documented progression or death due to any cause during or after the treatment period, whichever occurs first. Subjects who are still alive and progression free will be censored at the date of their last response assessment. The PFS curve will be estimated using KM method.

For the MDS cohort, transformation to AML and time to transformation to AML will be summarized. Time to transformation to AML is defined as the time from the date of randomization until the date the subject has documented transformation to AML. Subjects who do not transform to AML will be censored at the date of last follow-up, the date of death, or the date of study termination. Time to transformation to AML will be estimated using KM method.

9.7. Safety Analysis

All subjects in the safety population who receive at least one dose of any assigned IP, will be included in the safety analyses. Adverse events, vital sign measurements, physical exam findings, clinical laboratory data, ECG interpretations, pregnancy tests for FCBP, concomitant

medications and procedures will be tabulated and summarized by treatment arm, and cohort, as appropriate.

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 graded according to CTCAE Version 4.03 criteria (Appendix G).

The frequency of AEs will be tabulated by MedDRA SOC and PT. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events leading to discontinuation from treatment, events leading to dose reduction/interruption/delay, events classified as CTCAE Version 4.03 Grade 3 or higher, IP-related events, AESI, imAEs and serious AEs will be tabulated and listed separately. By-subject listings of all AEs, and AESIs, serious AEs, and their attributes will be provided.

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. Laboratory data will be graded according to CTCAE Version 4.03 criteria for select analytes unless otherwise specified. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by screening status. Clinically significant hematologic and nonhematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to CTCAE Version 4.03 will be listed and summarized.

Vital signs and ECG data will be summarized by cross-tabulations presenting normal and abnormal values by number of subjects at pre-and post-IP initiation.

Graphical displays will be provided where useful in the interpretation of results.

9.8. Interim Analysis

Interim analyses for futility purposes are planned for each cohort as described in Section 9.3. and will be based on the EE population.

9.9. Other Topics

9.9.1. Assessment of Pharmacokinetics [redacted]

9.9.1.1. Pharmacokinetic Analysis

Pharmacokinetic concentration data and summary statistics will be tabulated. Individual and mean concentration-time profiles will be generated. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow). The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. The results of such an analysis will be reported in a separate report.

[redacted]

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9.10. Study Committees

9.10.1. Data Monitoring Committee (DMC)

An external and independent DMC with multidisciplinary representation will be established to evaluate the results of the study.

The DMC will review the safety and the efficacy data of the study subjects after completion of Stage 1 of each cohort of the study.

The DMC chairman may convene formal DMC meetings if there are any unusual safety/efficacy concerns (eg, higher than expected transformation to AML rate observed in the study). The sponsor can also request a DMC review of the safety data if other events occur at a higher than expected rate. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter.

9.10.2. Steering Committee

A Steering Committee (SC) will be established by charter. The SC will be comprised of Study Investigators, and representatives of Celgene, and may include additional ad hoc members. The SC, separate from the DMC, will serve in an advisory capacity to the sponsor and recommend:

- Changes to the protocol or conduct of the study based upon emerging clinical or scientific data from this and/or other studies.
- Procedures to ensure the safety of subjects and integrity of study data.
- Procedures to meet the overall goals and objectives of the study.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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 eCRF (see Section 7.2.4 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 eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF 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 durvalumab or subcutaneous azacitidine 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 form until 28 days after the last dose of subcutaneous azacitidine (90 days after the last dose of durvalumab), or until the Treatment Discontinuation Visit, whichever is later as well as AML cases and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment (durvalumab, subcutaneous azacitidine).

Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

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

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

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

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

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

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

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the study treatment (durvalumab, subcutaneous azacitidine), action taken regarding the study treatment (durvalumab, subcutaneous azacitidine), and outcome.

10.2.2. 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 CTCAE, Version 4.03; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Adverse events that are not defined in CTCAE Version 4.03 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.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP (durvalumab, subcutaneous azacitidine) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

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

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

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

10.3. Abnormal Laboratory Values

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

- results in discontinuation from IP;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

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

10.4. Pregnancy

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

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated beta-human chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on study treatment, or within 90 days after last dose of study treatment (durvalumab, subcutaneous azacitidine), are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or 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 study treatment (durvalumab, subcutaneous azacitidine) 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.

10.4.2. Male Subjects

If a female partner of a male subject taking study treatment (durvalumab, subcutaneous azacitidine) 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 study treatment (durvalumab, subcutaneous

azacitidine) should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

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

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study treatment (durvalumab, subcutaneous azacitidine) that occur during the study (from the time the subject signs informed consent form until 28 days after the last dose of subcutaneous azacitidine (90 days after the last dose of durvalumab), whichever is later or any transformation to AML cases (MDS subjects) and those SAE made known to the Investigator at any time thereafter that are suspected of being related to study treatment (durvalumab, subcutaneous azacitidine). Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

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

10.5.1. 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.

10.6. 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 durvalumab and subcutaneous azacitidine based on the Investigator's Brochures.

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.

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 eCRF, reported to Celgene Drug Safety if meeting SAE reporting criteria (within 24 hours) and reported to regulatory authorities in the annual report.

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

- Any AE suspected of being related to the use of study treatment (durvalumab, subcutaneous azacitidine) 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 14.3 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.

10.7. Adverse Events of Special Interest

An Adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Adverse events of special interest 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 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 aetiology. 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 AE being an imAE, the Investigator should promptly contact the Medical Monitor.

Further information on risks (eg, presenting symptoms) can be found in the current version of the Investigator Brochure including guidelines for their evaluation and treatment.

10.7.1. Transformation to AML (for MDS Cohort only)

Transformation to AML will be monitored as an AESI 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 ICF until death, lost to follow-up, withdrawal of consent for further data collection, or study closure, whichever is later.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- Adverse Event
- Progressive disease
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Other (to be specified on the eCRF).

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

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

11.2. Study Discontinuation

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

- Screen failure
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Study Closure
- Other (to be specified on the eCRF).

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

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible sponsor's Clinical Research Physician (CRP)/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 sponsor's CRP/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 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 sponsor's CRP(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

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

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International 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.

13.2. Investigator Responsibilities

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

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

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

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

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

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

13.3. Subject Information and Informed Consent

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

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

13.4. Confidentiality

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

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

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene CRP/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.

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

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

Investigational product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include

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

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

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

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

13.7. 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 AEs 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.

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. 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 eCRFs or CD-ROM. There will be no analysis of data generated after the final data cut-off date. As such, any data generated after the final data cut-off date will be maintained in the source documents but will not need to be entered into the eCRF.

14.2. Data Management

Data will be collected via eCRF 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.

14.3. Record Retention

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

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, 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 or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

15.1. 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 Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, 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 eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

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

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

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

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18. APPENDICES

Appendix A: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
CCI [redacted]	[redacted]
ADL	Activity of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
CCI [redacted]	[redacted]
ASCT	Allogeneic stem cell transplantation
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BM	Bone marrow
BMA	Bone marrow aspirate
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CCR	Conventional care regimen
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CL	Clearance
Cmax	Maximum observed concentration
CMML	Chronic myelomonocytic leukemia
CML	Chronic myelogenous leukemia
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete blood recovery
CRP	Clinical Research Physician
CRS	Clinical Research Scientist

Abbreviation or Specialist Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
Ctrough	Trough concentration
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
CCI [redacted]	[redacted]
EMA	European Medicines Agency
EOI	End of infusion
CCI [redacted]	[redacted]
EOT	End of treatment
ESA	Erythropoietin-stimulating agent
EU	European Union
FAB	French-American-British
Fc	Fragment crystallizable
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
FT3/Free T3	Free Triiodothyronine
FT4/Free T4	Free Thyroxine
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase
GM-CSF	Granulocyte macrophage colony-stimulating factor
G-CSF	Granulocyte colony-stimulating factor
HBV	Hepatitis B virus

Abbreviation or Specialist Term	Explanation
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
Hgb	Hemoglobin
HI	Hematological improvement
HI-E	Hematological improvement – Erythroid response
HI-NE	Hematological improvement – Neutrophil response
HI-P	Hematological improvement – Platelet response
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMA	Hypomethylating agent
CCI [redacted]	[redacted]
HR	Hazard ratio
CCI [redacted]	[redacted]
[redacted]	[redacted]
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
IMiD®	A proprietary series of drugs with immunomodulatory and other properties
IND	Investigational New Drug
INR	International normalized ratio
INT-1	Intermediate-1
INT-2	Intermediate-2
IP	Investigational Product
IPSS	International prognostic scoring system
IPSS-R	Revised - International prognostic scoring system
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
IRT	Integrated Response Technology
ITT	Intent to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWG	International working group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LFTs	Liver Function Tests
CCI	[redacted]
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
mCR	marrow complete remission
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National comprehensive cancer network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OR	Overall response
OS	Overall survival
CCI	[redacted]
PCP	Pneumocystis pneumonia
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PFS	Progression-free survival
PK	Pharmacokinetics

Abbreviation or Specialist Term	Explanation
PR	Partial remission
CCI [redacted]	[redacted]
PS	Performance status
PT	Preferred term
PT/INR	Prothrombin time/international normalized ratio
QoL	Quality of life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RA	Refractory anemia
RARS	Refractory anemia with ring sideroblasts
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RBC	Red blood cell
CCI [redacted]	[redacted]
RFS	Relapse free survival
RNA	Ribonucleic acid
SAE	Serious adverse event
CCI [redacted]	[redacted]
SC	Steering committee
sc	Subcutaneous
CCI [redacted]	[redacted]
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedure
sPD-L1	Soluble program death ligand-1
SUSAR	Suspected unexpected serious adverse reaction
TB	Total bilirubin
TCR	T cell receptor
TEAE	Treatment emergent adverse event

Abbreviation or Specialist Term	Explanation
TIL	Tumor infiltrating lymphocyte
CCI [redacted]	[redacted]
TNF-α	Tumor necrosis factor-alpha
TNM	Tumor, node, metastases
TSA	Thrombopoiesis-stimulating agent
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization
WT	(Body) Weight

Appendix B: The World Health Organization (WHO) Classification of the Myeloid Neoplasms and Leukemia (Vardiman, 2009)

Category	Peripheral Blood	Bone Marrow
Refractory anemia (RA)	Anemia < 1% blasts < 1×10^9 monocytes	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts < 15% sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia < 1% blasts < 1×10^9 monocytes	Erythroid dysplasia < 10 % myeloid or megakaryocytic dysplasia < 5% blasts > 15% sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Bi-or pancytopenia < 1% blasts < 1×10^9 monocytes	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts < 15% sideroblasts
Refractory anemia with multilineage dysplasia and ring sideroblasts (RCMD-RS)	Bi-or pancytopenia < 1% blasts < 1×10^9 monocytes	Dysplasia in > 10% of the cells in 2 or more cell lines < 5% blasts > 15% sideroblasts
Refractory anemia with excess blasts type I & II (RAEB-1 & RAEB II)	Cytopenia Type I: 1-5% blasts Type II: 5-19% blasts	Uni- or multilineage dysplasia Type I 5-9% blasts Type II 10-19% blasts
5q- syndrome	Anemia Normal or elevated platelets < 5% blasts	Normal or increased megakaryocytes < 5% blasts
MDS unclassified (MDS-U)	Cytopenia < 1% blasts	Unilineage dysplasia of myeloid or megakaryocytic line < 5% blasts
Myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN) - CMML* - MDS/MPN-U		

CMML = chronic myelomonocytic leukemia; MPN-U = myeloproliferative neoplasms unclassified

* For this study CMML subjects will be excluded.

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 C: International Prognostic Scoring System for MDS (Greenberg, 1997)

	Survival and AML Evolution Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Marrow Blasts (%)	< 5	5 to 10	n/a	11 to 20	21 to 30
Karyotype	Good Normal or any 1 of: -Y del(5q) del(20q)	Intermediate Any other chromosome anomaly	Poor chromosome 7 anomalies; Complex: ≥ 3 chromosome anomalies	n/a	n/a
Cytopenias: Neutrophil count < 1800/μL Platelets < 100,000/μL Hb < 10 g/dL	0 or 1	2 or 3	n/a	n/a	n/a

AML = acute myeloid leukemia; Hb = hemoglobin

The total IPSS score and IPSS risk category are calculated as the sum of three individual scores based on the marrow blast percentage, the karyotype, and the number of cytopenias.

Risk Category	**Combined Score = Sum of Marrow blast + Karyotype + Cytopenia Score**
Low	0
Intermediate-1	0.5 to 1.0
Intermediate-2	1.5 to 2.0
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 Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006)

Altering Disease Natural History	
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted [a] Peripheral blood: - Hemoglobin ≥ 11 g/dL - Platelets ≥ 100 × 10^9/L - Neutrophils ≥ 1.0 × 10^9/L - Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment Disease progression characterized by worsening of cytopenias, increase in % of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Disease Progression (PD)	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5% - 10% blasts: ≥ 50% increase in blasts to > 10% blasts • 10% - 20% blasts: ≥ 50% increase in blasts to > 20% blasts • 20% - 30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 2 g/dL • Transfusion dependence

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

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 D: International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006) (Continued)

Altering Disease Natural History	
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	At least one of the following: • Return to pretreatment bone marrow blast % • 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

Hematological Improvement (HI)	
Erythroid response (HI-E) (Pretreatment < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion evaluation
Platelet response (HI-P) (Pretreatment < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
Neutrophil response (HI-N) (Pretreatment < 1.0×10^9/L)	At least 100% increase and an absolute increase of > 0.5×10^9/L
Progression/relapse after HI	At least one of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

AML = acute myeloid leukemia; Hgb = hemoglobin; RBC = red blood cell
Source: Cheson BD, Greenberg PL, Bennett JM, Löwenberg 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 E: ECOG Performance Status Scale

The ECOG Performance Status Scale is used to score a subject's quality of life through evaluation, by a health professional, of daily activities and how those activities are affected by the disease of the subject.

Score	Description
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 housework, 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: New York Heart Association Classification for Congestive Heart Failure

Classification of Heart Failure

Class	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 G: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

Currently active minor version of NCI CTCAE, Version 4.03:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix H: Revised International Prognostic Scoring System for MDS – IPSS-R (Greenberg, 2012)

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	-	Inter-mediate	Poor	Very Poor
Bone Marrow Blast (%)	≤ 2	-	> 2 - < 5	-	5 - 10	> 10	-
Hemoglobin (g/dL)	≥10	-	8 - < 10	<8	-	-	-
Platelets (× 10^9/L)	≥100	50 - < 100	< 50	-	-	-	-
ANC (× 10^9/L)	≥0.8	< 0.8	-	-	-	-	-

ANC = absolute neutrophil count

The total IPSS-R score is calculated as the sum of the cytogenetics, bone marrow blast percentage, hemoglobin, platelets and ANC individual scores.

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

Prognostic variable	No. pts	Very Low	Low	Intermediate	High	Very High
Patients (%)	7012	19%	38%	20%	13%	10%
Median Overall Survival (years)	-	8.8	5.3	3.0	1.6	0.8
Median time to 25% AML evolution	-	Not reached	10.8	3.2	1.4	0.7

Source: Greenberg, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. 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.

Appendix I: The World Health Organization (WHO) Classification of Acute Myeloid Leukemia (Swerdlow, 2008)

Acute myeloid leukemia with recurrent genetic abnormalities
Acute myeloid leukemia with t(8;21)(q22;q22); (RUNX1-RUNX1T1)
Acute myeloid leukemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); (CBFB-MYH11)
Acute promyelocytic leukemia with t(15;17)(q22;q12); (PML-RARA)
Acute myeloid leukemia with t(9;11)(p22;q23); MLLT3-MLL
Acute myeloid leukemia with t(6;9)(p23q34); DEK-NUP214
Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q26.2); RPN1-EVI1
Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
Acute myeloid leukemia with gene mutations
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise categorized
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis

IARC = International Agency for Research on Cancer; WHO = World Health Organization
Source: Swerdlow SH, Campo E, Harris HL, et al. eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press: 2008; 109-139.

Appendix J: Risk Status Based on Cytogenetics for Acute Myeloid Leukemia

Risk Groups

Risk Status	Cytogenetics	Molecular Abnormalities[a]
Better-risk	inv(16)[b,c] t(16;16)[b] t(8;21)[b] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT [d] mutation
Poor-risk	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[e]	Normal cytogenetics: with FLT3-ITD mutation [f]

[a] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[b] Other cytogenetic abnormalities in addition to these finding do not alter risk status.

[c] Paschka P, Du J, Schlenk RF, Gaidzik VI, Bullinger L, Corbacioglu A, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013; 121:170-177.

[d] Emerging data indicates the presence of c-KIT mutation in subjects with t(8;21), and to a lesser extent, inv(16), confers a high risk of relapse. These subjects should be considered for clinical trials, if available.

[e] For Philadelphia+ acute myeloid leukemia (AML) t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia (CML), with addition of tyrosine kinase inhibitors. These subjects are excluded from study entry.

[f] FLT3-ITD mutations are considered to confer a significant poor outcome in subjects with normal karyotype, and these subjects should be considered for clinical trials where available. There is controversy as whether FLT3-TKD mutations carry equally poor prognosis

Source:
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia. National Comprehensive Cancer Network website. Available at http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed 05 Aug 2015.

Appendix K: Modified International Working Group AML Response Criteria (Cheson, 2003)

Hematologic Response According to IWG Criteria for AML

Category	Definition
Morphologic Complete Remission (CR)	The following conditions should be met: • ANC ≥ 1,000/μL[b]; • Platelet count ≥ 100,000/μL; • The bone marrow should contain less than 5% blast cells; • Auer rods should not be detectable; • Independent of transfusions
Morphologic Complete Remission with Incomplete Blood Count Recovery (CRi)	Defined as a morphologic complete remission but the ANC count may be < 1,000/μL and/or the platelet count may be < 100,000/μL.
Cytogenetic Complete Remission (CRc)	Defined as morphologic complete remission with a reversion to a normal karyotype.
Partial Remission (PR)	Defined as an ANC ≥ 1,000/μL and platelet count ≥ 100,000/μL with a > 50% decrease in the percentage of bone marrow blasts to 5% to 25% (a blast count value of ≤ 5% may also be considered a partial remission if Auer rods are present).[a, b]
Relapse after CR or CRi	Defined as 1) the reappearance of > 5% blasts in the peripheral blood, or 2) a single finding of > 15% blasts in the bone marrow. All of the above occurrences should be attributed to relapse following CR or CRi and not attributable to another cause (eg, bone marrow regeneration after consolidation therapy)[b].
Treatment Failure	**Aplasia**: Subject survives ≥ 7 days post chemotherapy; death while cytopenic, with aplastic bone marrow. **Indeterminate Cause:** • Subjects who die < 7 days posttherapy • Subjects who die ≥ 7 days posttherapy with no peripheral blood blasts, but no bone marrow examination [b] • Subjects who die without completing the first course of therapy

Category	Definition
Progressive Disease[b]	Defined as: 1) a > 50% increase in bone marrow blast count percentage from the baseline bone marrow blast count that persists for at least 2 bone marrow assessments separated by at least 1 month, unless the baseline bone marrow blast count is > 70%, in which case, a finding of > 70% blasts that persists for 2 postbaseline bone marrow assessments separated by at least 1 month would be considered progression, or 2) a doubling of the baseline absolute peripheral blood blast count that persists for at least 7 days and the final absolute peripheral blood blast count is > 10×10^9/L. The date of progressive disease is defined as the first date that there was either a > 50% increase in bone marrow blast count from baseline, a persistence of bone marrow blasts > 70% in subjects with a baseline bone marrow blast count of > 70%, or a doubling of the peripheral blood blast count.

ANC = absolute neutrophil count

[a] If the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%.

[b] Modification to IWG response criteria.

Notes: Deletions to the IWG response criteria are not shown.

Source: Cheson BD, Bennett JM, Kopecky KJ, et al. Revised Recommendations of the International Working Group for diagnosis, Standardization of response Criteria, Treatment Outcomes, and reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.

CCI

CCI

Appendix M: Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Nonimmune–mediated Reactions (MEDI4736) 01 Nov 2017 Version

General Considerations	
Dose Modifications	**Toxicity Management**
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 regimen 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. 3. Doses of prednisone are at ≤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. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold IP/study regimen, and if complete work up shows no evidence of pancreatitis, IP/study regimen may be continued or resumed.	It is recommended that management of immune-mediated adverse events (imAEs) follows 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 (e.g., disease progression, concomitant medications, and infections) 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 (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., 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 [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs

General Considerations	
Dose Modifications	**Toxicity Management**
IP Note: IP/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., 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 – e.g., 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 (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	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 – e.g., 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/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of IP/study regimen 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; IV intravenous; NCI National Cancer Institute; PO By mouth.

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 (e.g., 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 (e.g., 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 [e.g., tracheostomy or intubation])	Permanently discontinue IP/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the subject. – Supportive care (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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 (i.e., 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 (i.e., 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 (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., 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 (e.g., 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 (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., 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 (e.g., 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 (e.g., 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 (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., 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 (e.g., 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 (e.g., IV IG).
	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 (e.g., IV IG). – 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 (e.g., 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 (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
	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 (e.g., 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 IV IG. 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
	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 IV IG. 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
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 (e.g., 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 (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., 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-	- 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 (e.g., 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 (e.g., 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**
	threatening consequences; urgent intervention indicated (e.g., 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.

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, creatine kinase, aldolase, LDH, BUN/creatinine, 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 (i.e., 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 (e.g., 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., 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 (e.g., 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 (e.g., 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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			using infliximab. – Consider whether subject may require IV IG, 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]

[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.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; 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.

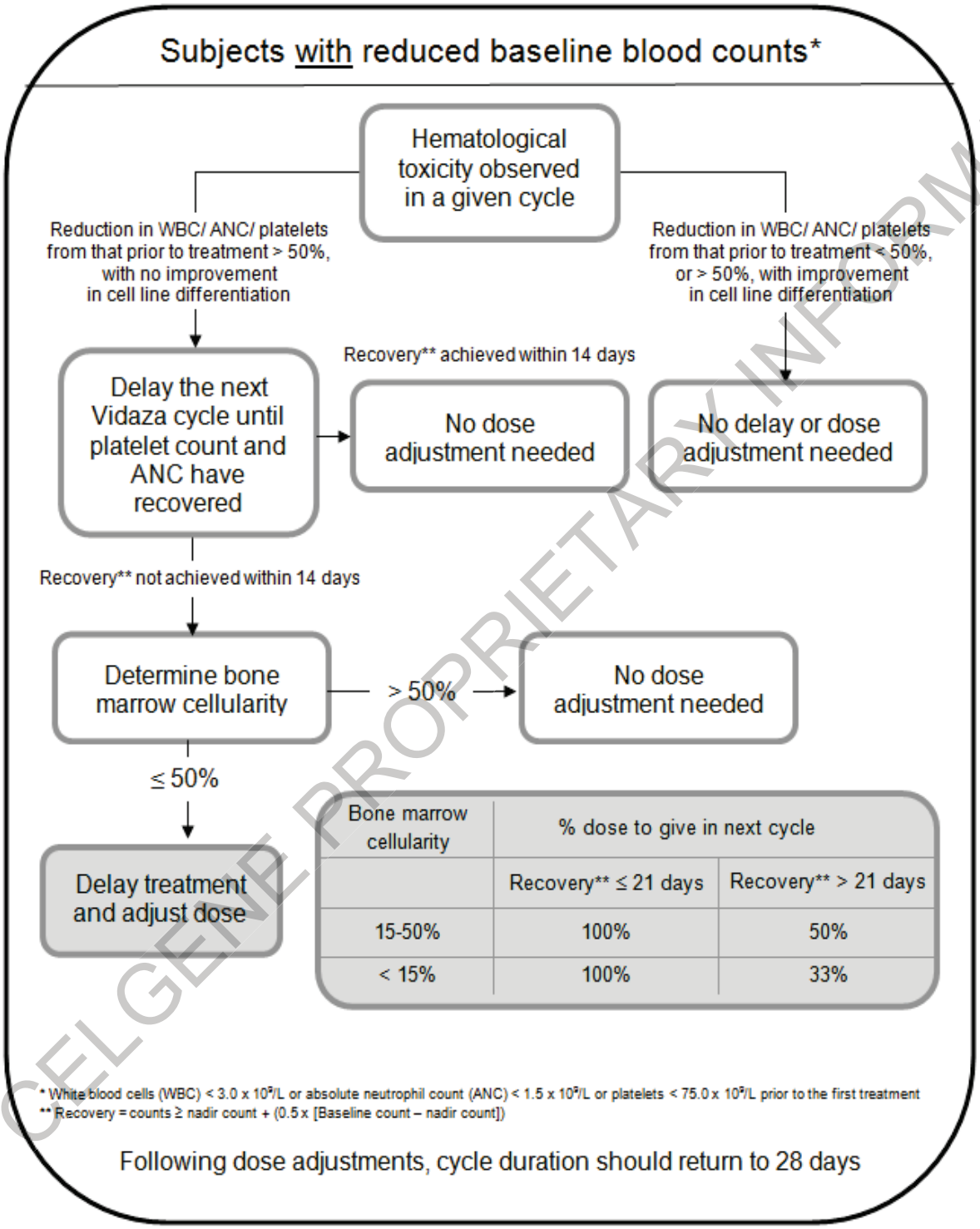
Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor subjects for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of IP/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For 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.	**For Grade 1 or 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 3 or 4	**For Grade 3 or 4:** Permanently discontinue IP/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

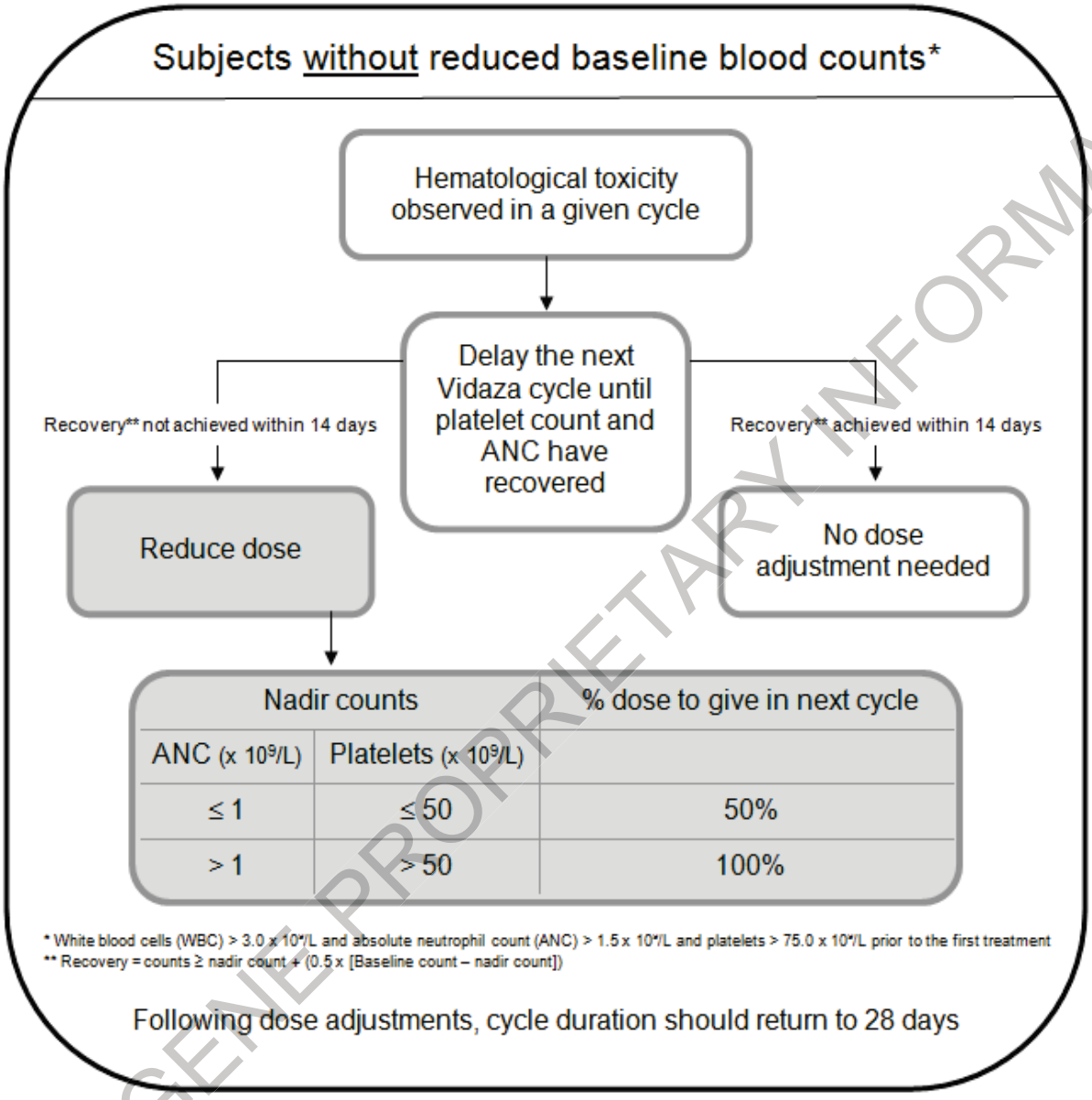
Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities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

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.
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."

Appendix N1: Azacitidine Dose Modifications due to Hematologic Toxicity – Subjects with Reduced Baseline Blood Counts



Appendix N2: Azacitidine Dose Modifications due to Hematologic Toxicity – Subjects without Reduced Baseline Blood Counts



Appendix O: Optional Extension Phase

Subject Eligibility

At the end of trial (Section 3.3), at the Investigator's discretion, subjects who continue to benefit from treatment with subcutaneous azacitidine and/or durvalumab, without unacceptable toxicities and who have met criteria for treatment continuation may continue to receive subcutaneous azacitidine and/or durvalumab provided by the sponsor through this protocol. (See Safety Review and Update, below)

At the Investigator's discretion, subjects meeting all the following continuation criteria are eligible to enter the optional extension phase:

1. Subjects who have signed the addendum informed consent for the extension phase of the study.
2. Subjects who do not meet any of the following treatment discontinuation criteria (see Section 11):
   - Adverse Event
   - Progressive disease
   - Withdrawal by subject
   - Lost to follow-up
   - Pregnancy.
3. Subjects who continue to show clinical benefit from study treatment as per the Investigator's assessment (See Section 6.7.4 for MDS and AML continuation criteria).

Subjects will start the extension phase at the time of the next regularly scheduled dosing cycle for study drug azacitidine or azacitidine and durvalumab.

Safety Review and Update

The study has been closely monitored by the independent Data Monitoring Committee (DMC) as described in the protocol. Following a planned and recent review (December 2018) of both safety and efficacy data, the DMC noted that that there may not be an added benefit of durvalumab plus azacitidine in terms of efficacy, and there exists a potential for late events such as cytopenias and immune mediated adverse events (ImAEs). Accordingly, the DMC advised to discontinue administration of durvalumab and continue only azacitidine for all ongoing study subjects. Before implementing DMC recommendation, a thorough review of safety and efficacy data of all ongoing subjects was conducted along with a literature review of long-term safety on Durvalumab. No new safety concerns were identified. This was presented to the DMC in January 2019.

The DMC assessed individual safety and efficacy data for all ongoing subjects on long-term therapy (≥ 12 cycles). Upon review of the additional data, the DMC recognized that individual subjects may be impacted by indiscriminate discontinuation of durvalumab. In their recommendation following the second meeting, the DMC noted that Celgene may continue treatment with durvalumab in subjects who are actively being treated on the combination arm

and wish to continue following careful review of the efficacy and toxicity data and the DMC's report for the study.

Celgene, upon careful review of all safety and efficacy data and risk benefit ratio, which remains acceptable, decided to allow the continuation of durvalumab and azacitidine for those subjects who wish to continue the combination treatment based on a discussion with their investigator or continue on azacitidine alone. Subjects on azacitidine monotherapy who continue to receive clinical benefit will be allowed to continue treatment as planned. Celgene will continue to monitor safety including late events in subjects who are actively receiving durvalumab in the combination treatment arm of both MDS and AML cohorts.

Dosage and Regimen During the Extension Phase

The dosing and schedule in the extension phase should follow the same treatment administration and schedule as outlined in the protocol (Section 7.2). The dose for the first treatment cycle in the extension phase should be the same dose the subject received during the final treatment cycle prior to the extension.

Extension Phase Treatment Cycles

Cycles should be repeated every 28 days. For subjects on combination therapy, durvalumab is administered Day 1 of each cycle. Azacitidine is administered Days 1 to 7 of each cycle. Azacitidine is to be administered one hour after completion of the durvalumab dose on Day 1. Dosage delay or reduction may be necessary as described below.

Dose Modification and Toxicity Management

Please follow the Dose Modification and Toxicity Management guidance as outlined in the protocol (Section 7.2.2, Appendix N1, and Appendix N2).

Adverse Event Reporting

Only SAEs should be reported (see Section 10.5 of the protocol for SAE reporting guidance). 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 (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports. Serious Adverse Events will NOT be entered into an eCRF.

Concomitant Medications

All concomitant medications that are necessary for the subject's welfare and are unlikely to interfere with azacitidine or durvalumab may be given at the Investigator's discretion during the extension phase. However, treatment with another investigational medication is not permitted.

Monitoring of Subjects

The subjects included in the extension phase will be monitored according to the standard of care at the site. Source documentation (medical records, laboratory reports, investigator notes, disease assessments, etc) needs to be complete and accessible for review as required. Data collection in the eCRF will stop, but the IRT system remains to track study visits and IP accountability.

Investigator's Responsibility

1. Document and report only serious adverse events and pregnancies as required by the protocol. A completed SAE and/or pregnancy form must be faxed to Celgene Drug Safety, as detailed in the Serious Adverse Event Report Form Completion Guidelines or Pregnancy Report Form Completion Guidelines, immediately (ie, within 24 hours of the Investigator's knowledge of the event). (see Section 10.5).
2. The subject should stop treatment if any of the following occur:
    a. Additional investigational treatment is started
    b. Subject is no longer receiving clinical benefit, as per Investigator discretion
    c. Subject withdraws consent
    d. At the specific request of the sponsor or its authorized representative.
3. The Investigator must be available for a monitoring visit (if necessary) and allow the sponsor access to all medical records.
4. The Investigator will maintain documentation in the subjects' medical chart for the following:
    a. Informed consent
    b. Adverse events and Serious Adverse Events to allow for monitoring of possible late events
    c. Dosing information (date of administration, dose administered)
    d. Extension Phase termination date and reason.

Note: There will not be an eCRF for data collection in the extension phase of this study. The only data collection for reporting to the sponsor is for SAEs. These will be reported to the sponsor Safety department as outlined in the protocol (See Section 10.5). Therefore, any reference to eCRF entries in the protocol are no longer applicable after the final analysis cut-off date.

End of the Extension Phase

The extension phase will be considered complete when the last subject included in this phase completes their last treatment cycle and has been followed-up as per the site standard of care. Subjects should be followed for safety up to 28 days for azacitidine and up to 90 days for durvalumab after the last dose of corresponding study drug.

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: Wednesday, 13 March 2019, 11:01 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

The primary update via this amendment is the addition of Appendix O that describes the extension phase. The purpose of this amendment is to provide an extension to the study to allow patients who were benefiting from treatment to continue treatment with either azacitidine alone or azacitidine and durvalumab (depending on their randomization in the main study) now that the study is ending. The only change to the body of the protocol is in Section 3.3.

Subjects who enter the extension phase will continue to be seen and treated by the investigator. The amendment does not require any laboratory work, testing or assessment other than investigator reporting of serious adverse events SAEs as stipulated under the full protocol. Subjects will be receiving standard of care for their condition.

In addition, the independent data monitoring committee (DMC) reviewed the safety and efficacy results as described in the protocol in December 2018 and January 2019. Their initial recommendation was to stop on-study durvalumab treatment for all patients and to continue with AZA alone in both arms. However, they recognized that individual patients may be impacted by indiscriminate drug discontinuation, both in a positive direction and in a negative direction due to the chance of serious adverse events when continuing with durvalumab. Therefore, they noted that Celgene may wish to continue treatment with durvalumab in patients who are actively being treated on the combination arm and wish to continue following careful review of the efficacy and toxicity data and the DMC's report on the MEDI4736-MDS-001study.

Title Page (updated)

1. Sponsor address updated.

Section 3.3 (updated)

2. Includes a reference to Appendix O.
3. Procedural directions for subjects not entering the extension.

Section 14.1 (updated)

1. Statement to clarify that data analysis will not be conducted on data generated after the final data cut-off date and therefore this data to be recorded in the source documents and not in the electronic case report form (eCRF).

Appendix O (new)

1. Defines eligibility for subject enrollment into the extension based on the investigator assessment.
2. Places subjects in a standard of care situation. Celgene will provide the investigational product (IP), but the office visits and all other procedures (laboratory assessments, bone marrow biopsy/aspirate, etc) are at the discretion of the investigator and are not part of the protocol.
3. Establishes the documentation that is required in the subjects' medical chart.
    a. There will not be a clinical database; no data collected in an eCRF

   b. Investigator will document all adverse events and report to the sponsor only the serious adverse events and pregnancies as required by the main protocol.
4. The Extension phase will end when the last subject included in this phase completes their last treatment cycle and has been followed-up as per the site standard of care.
5. In addition, Appendix O details the following:
   a. Dosing, dose modification and treatment cycles
   b. Adverse event reporting
   c. Investigator's responsibilities
   d. Safety Review and Update – includes the DMC reviews, Celgene review of safety in long-term treatment (≥12 cycles), and the decision to continue treating subjects with durvalumab plus azacitidine for those subjects who wish to continue the combination treatment based on a discussion with their investigator or continue on azacitidine alone.

1. JUSTIFICATION FOR AMENDMENT

This protocol was amended as follows:

CCI [redacted]

2. Update of the Therapeutic Area Head on the Celgene Therapeutic Area Head Signature Page
3. The dosing modification and toxicity management guidelines (Appendix M of the protocol) have been updated following a durvalumab investigator's brochure (IB) update.
4. To be consistent with Appendix M, the term, "immune-related adverse event", (abbreviated as irAE) has been changed to "immune-mediated adverse event", (abbreviated as imAE), and the term, "immune-related etiology", has been changed to "immune-mediated etiology" throughout the protocol text and in Appendix A, Table of Abbreviations.
5. Editorial updates were made throughout the protocol to correct superscript formatting (updating "109" to "10^9").

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 1.0 was written to provide clarification language and ensure the protocol is more precise on certain aspects.

Significant changes included in this amendment are summarized below:

- Clarification on the cytogenetic risk stratification:

  By opposing intermediate versus poor and very poor, it was misleading in the very few occasions where subjects with good/very good cytogenetic risk were enrolled. This modification will have no impact on stratification in Interactive Response Technology (IRT), and no impact on study population. Revised wording: "Very good, good and intermediate versus poor and very poor for MDS (Appendix H)".

  Revised sections: Protocol Summary, Section 3.2.2 "Treatment Phase", Section 9.1 "Overview".

- Clarification on good cytogenetic risk AML patients. As per National Comprehensive Cancer Network (NCCN) guidelines, document that is used for reference, Good cytogenetic risk patients are to be excluded from this protocol, unless associated with c-kit mutation. Clarification has been added to allow recruitment of such patients.

  Revised section: Section 4.2.2 "Exclusion criteria No. 33".

- Addition of an extra exclusion criteria, based on Investigator feedback. There has been one case of worsening Sweet Syndrome while on study treatment. As this is a rare condition, this should not affect patient population and recruitment.

  Revised section: Section 4.2.2 "Exclusion criteria No. 35".

- Table of events has been updated to reflect the following modifications:

  Vital signs will be required at each visit. The Clinical team wants to reinforce patients' monitoring, so everytime a patient will come for a visit (eg, for blood draw), patients will have their vital signs checked (blood pressure, pulse, body temperature and respiratory rate) by the principal investigator (PI)/nurse.

  Chemistry tests frequency increased from cycle 3 onwards. Starting cycle 3 onwards the chemistry test was scheduled on Day 1 of each cycle. In order to increase patients' monitoring the decision was made to perform chemistry tests on Day 1 and Day 15 of all cycles.

  Bone marrow aspirate for disease assessment. The window for bone marrow collection has been extended to allow more flexibility. Instead of collecting bone marrow aspirate on Day 22 of the concerned cycles +/- 3 days, it will be required to perform the bone marrow aspirate prior to the next cycle.

  Revised sections: Section 5 "Table of events", Footnote p of the Table of events, Section 6.6.3 "Physical examination, Vital signs and Weight", Section 6.6.6.2 "Biochemistry parameters" and Section 6.7.1 "Bone Marrow aspirate".

- Patient population in the statistical section has been made more precise, to clarify that the efficacy evaluable population is the intent to treat (ITT) population who completed 6

cycles of treatment, unless they have established an earlier response or who discontinued study due to death or disease progression. Precision has also been made for the interim analyses for both cohorts. The subjects part of these interim analyses will be subjects who have completed 6 cycles of assigned treatment (ie, for arm A, 6 cycles of durvalumab and azacitidine, arm B, 6 cycles of azacitidine), unless they have established an earlier response or discontinued due to death or disease progression.

This clarification has been made to ensure that interim conclusions are made based on subjects who have received 6 cycles of the assigned study treatment and were sufficiently exposed.

Revised sections: Section 9.2.2 "Efficacy Evaluable Population", Section 9.3.1 "Myelodysplastic Cohort", Section 9.3.2 "Acute Myeloid Leukemia Cohort".

- Adverse events of special interest (AESI) definition has been further defined to include Astra Zenecca-Medimmune recommended language for durvalumab AESIs and harmonized with other durvalumab protocols.

  Revised section: Section 10.7 "Adverse Events of Special Interest".

The amendment also includes several other updates, clarifications and corrections:

- Clinical Research Physician (CRP) name change:

  PPD has been replaced by PPD

  Revised sections: Medical Monitor/Emergency Contact Information.

- Wherever possible, the term "patient" has been replaced by "subjects"
- Change in contraception wordings under Inclusion Criteria to comply with Clinical Trial Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials.

  Revised section: Section 4.2.1 "Inclusion criteria No. 3b and No. 4".

- Modification of the wording describing the 2 stages of recruitment. The sentence "determining whether that cohort proceeds to Stage 2" has been removed. The reason is that given the actual recruitment, it is likely that stage 2 of the cohort will be already completed at the time of interim analysis conclusions.

  Revised sections: Protocol Summary, Section 3.1 "Study design", Section 9.1 "Overview".

- Clarification on sample size: Addition of the word "evaluable" patients. This will allow for a slight over recruitment to replace those not evaluable patients.

  Revised sections: Protocol Summary, Section 4.1 "Number of subjects", Section 9.3.1 "Myelodysplastic Cohort", Section 9.3.2 "Acute Myeloid Leukemia Cohort".

- Revision of the introduction to reflect Azacitidine Investigator Brochure updates.

  Revised section: Section 1.3.1 "Clinical Safety Experience with Azacitidine".

- Revision of the introduction to reflect Durvalumab Investigator Brochure updates.

  Revised sections: Section 1.4.1 "Durvalumab Experience in Solid Tumors", Section 1.4.2 "Durvalumab Experience in Myelodysplastic Syndromes.

- Clarification on the granulocyte colony-stimulating factor (G-CSF) use prior to study entry. It is allowed providing a wash-out period of 28 days is respected.

  Revised section: Section 4.2.2 "Exclusion criteria No. 5".

- Clarification on Hydroxyurea use prior to study entry. It is prohibited within the 2 weeks prior to obtaining the screening hematology sample and also prior to the first dose of investigational product (IP).

  Revised section: Section 4.2.2 "Exclusion criteria No. 26 and No. 30".

- Dose modification and toxicity management wording for azacitidine has been revised. Flexible language has been added to let the investigator decide on dose modification taking into consideration the patient's condition. Wording must be considered more as a guidance and is to be followed at the investigator's discretion.

  Revised section: Section 7.2.2.1 "Azacitidine".

- Update to Durvalumab Treatment Modification and Toxicity Management Guidelines (Appendix M).