DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-486-MDS-006

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

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STATISTICAL ANALYSIS PLAN

A Phase 2, International, Multicenter, Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of CC-486 (Oral Azacitidine) Alone and in Combination with Durvalumab (Medi4736) in Subjects with Myelodysplastic Syndromes who fail to achieve an objective response to treatment with Azacitidine for injection or Decitabine

INVESTIGATIONAL PRODUCT (IP):	CC-486 (oral azacitidine) Durvalumab (MEDI4736)
PROTOCOL NUMBER:	CC-486-MDS-006
DATE FINAL:	30 June 2014
DATE AMENDMENT #1.0 FINAL	08 Sep 2015
EudraCT NUMBER:	2014-002675-29
IND NUMBER:	074618
SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue, Summit, NJ 07901

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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	A Phase 2, International, Multicenter, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy and Safety of CC-486 (oral azacitidine) Alone and in Combination With Durvalumab (MEDI4736) in Subjects With Myelodysplastic Syndromes Who Fail to Achieve an Objective Response to Treatment With Azacitidine for Injection or Decitabine
SAP VERSION, DATE	Version 1.1, dd-Jul-2015
SAP AUTHOR	PPD (Printed Name and Title) — PPD Date: 2020.03.23 14:20:17 -04'00' (Signature and Date)
PROTOCOL TITLE	A Phase 2, International, Multicenter, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy and Safety of CC-486 (oral azacitidine) Alone and in Combination With Durvalumab (MEDI4736) in Subjects With Myelodysplastic Syndromes Who Fail to Achieve an Objective Response to Treatment With Azacitidine for Injection or Decitabine
INVESTIGATIONAL PRODUCT	CC-486 (oral azacitidine), Durvalumab (MEDI4736)
PROTOCOL NUMBER	CC-486-MDS-006
PROTOCOL VERSION, DATE	08 September 2015
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature PPD PPD Date: 2020.03.23 13:31:46 -04'00'

Printed Name _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature PPD

Printed Name _____ Date 19-MAR-2020

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HISTORY OF AMENDMENTS

Amendment number	Date of amendment	Rationale of amendment	Impact to statistical analysis and descriptions
#1	June, 2019	The PK analyses were planned but not conducted in the combination arm which was stopped since the optimal combination dose could not be determined. Only a few subjects were enrolled in the combination arm who agreed to PK sample collection and due to the limited samples collected, the PK TLGs will not be generated.	The PK TLG will not be produced.
#2	Mar 19, 2020	The AESI list had been updated to reflect the new search paths.	The AESI related tables and listings will be updated.

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	adverse event
AML	acute myelogenous leukemia
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BSA	body surface area
CI	confidence interval
CR	complete remission
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data management committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ESA	erythropoiesis-stimulating agents
FCBP	female of child-bearing potential
HI	hematologic improvement
HI-E	hematologic improvement erythroid
HI-N	hematologic improvement neutrophil
HI-P	hematologic improvement platelet
HRQoL	health-related quality-of-life
IC	informed consent
INT-1	intermediate-1
IP	Investigational Product
IPSS	International Prognostic Scoring System
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWG	International Working Group

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KM	Kaplan-Meier
mCR	Marrow CR
MDS	myelodysplastic syndromes
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI	National Cancer Institute
OS	overall survival
PD	pharmacodynamic/pharmacodynamic
PK	pharmacokinetics/pharmacokinetic
PR	partial remission
pRBC	packed red blood cell
QD	once daily
RBC	red blood cell
ROW	rest of world
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SC	subcutaneously/subcutaneous
SD	stable disease
SOC	system organ class
TEAE	treatment emergent adverse event
WBC	white blood cell
WHO	World Health Organization

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2. INTRODUCTION

This statistical analysis plan (SAP) describes the scope and methodologies of statistical data analyses and presentations of the analytical results for Celgene protocol CC-486-MDS-006: "A Phase 2, International, Multicenter, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy and Safety of CC-486 (Oral Azacitidine) Alone and in Combination With Durvalumab (MEDI4736) in Subjects With Myelodysplastic Syndromes Who Fail to Achieve an Objective Response to Treatment With Azacitidine for Injection or Decitabine."

This SAP contains brief descriptions of the investigational plan, study subject disposition, demographics and baseline characteristics of study subjects, treatment exposure analysis, concomitant medication analysis, and general statistical considerations for the analysis of efficacy and safety data.

The study consists of four study phases: Screening, Safety Run-in, Randomized Treatment, and Follow-up. The objective of the safety run-in phase is to determine the dose regimen for the monotherapy with CC-486 and the combination therapy with CC-486 + durvalumab using the 3+3 experimental design. After the determination of dose regimen for monotherapy or combination therapy, the study will enter the randomization treatment phase utilizes the Simon's two-stage design method for four patient cohorts, namely, the stable disease (SD) cohort treated with CC-486, the progressive disease (PD) cohort treated with CC-486, the SD cohort treated with CC-486 + durvalumab, and the PD cohort treated with CC-486 + durvalumab.

The analysis will be performed for the first stage initially to determine whether a cohort should continue to the second stage. Further analysis at the end of second stage will be conducted for the cohorts which enter the second stage of the study. Subjects will be followed for potential safety issues after they leave the safety run-in or treatment phase. The analytical results of efficacy and safety data for all cohorts will be presented together in a report with tables and listings.

This SAP will be finalized and signed-off prior to the clinical database is locked for the interim analysis or the first stage clinical data analysis, whichever occurs sooner, of any patient cohort. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis Software (SAS)® Version 9.3 or higher.

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3. OBJECTIVES

3.1. Primary Objective

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

3.2. Secondary Objectives

The secondary objectives of the study are to:

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

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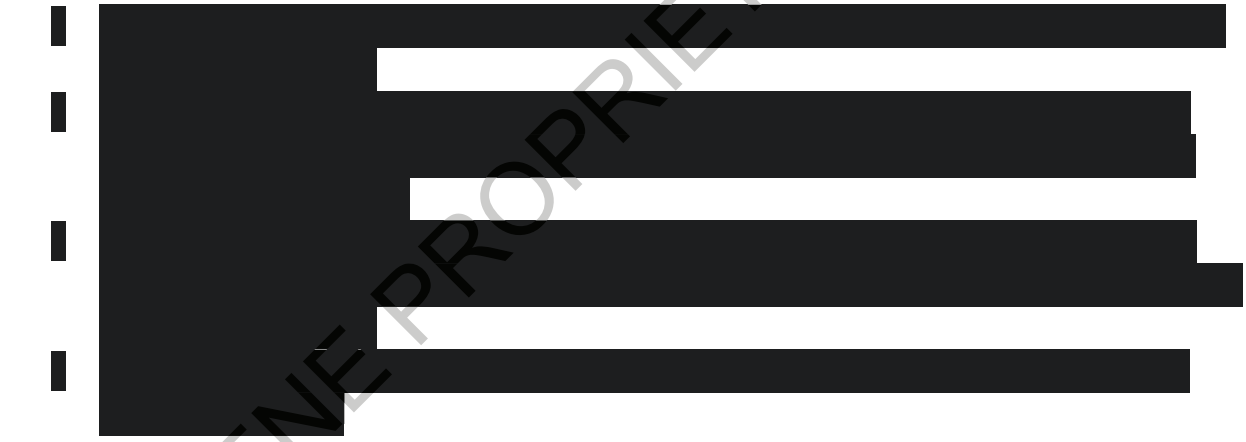

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4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, international, multicenter, randomized, parallel group, open-label study consisting of 4 study phases: *Screening, Safety Run-in, Randomized Treatment*, and *Follow-up*.

Safety Run-In Phase:

Safety Run-in will use the 3+3 design to explore the possible dose regimen for the monotherapy and combination therapy as well as the corresponding safety and tolerability profiles. Safety run-in will be conducted in sequential order with monotherapy first and then the combination therapy. The number of subjects needed for this phase will depend on the safety and tolerability findings

Randomized Treatment Phase:

The randomized treatment phase of the study will be conducted in 2 stages using Simon's two-stages design. Following identification of dose and schedule in the safety run-in of a treatment arm, enrollment for Stage 1 of the treatment phase may begin.

Eligible subjects will be randomized to one of two open treatment arms. In the event that combination therapy cohorts are not ready to enroll for this phase, the available subjects will be enrolled into the monotherapy cohorts. The randomization with 1:1 ratio will start when safety run-in phase is finished for both monotherapy and combination therapy arms. In the event that one arm has completed enrollment, all available subjects thereafter will be enrolled into the other arm. The randomization will be stratified according to subject's disease status, namely, Stable Disease (SD) or Progressive Disease (PD), at study entry.

Based on subject's disease status and the treatments, there will be four cohorts: (1) SD with Monotherapy, (2) PD with Monotherapy, (3) SD with Combination therapy, and (4) PD with Combination therapy.

During Stage 1, if a cohort is awaiting the decision to continue to Stage 2 pending on the response evaluation while the other cohort of the same patient classification is open for enrollment, available patients will be assigned to the cohort with open enrollment without randomization. If both cohorts of the same patient classification are waiting for response evaluations, enrollment of that patient classification will be temporarily halted.

The total number of subjects for the randomized treatment phase will range from approximately 64 (at Stage 1) to 164 (Stage 1 plus Stage 2) for the four subject cohorts. More subjects can potentially be recruited for replacement of non-evaluable subjects, if needed. Details can be found in the Sample Size section.

PK Sampling:

Blood samples for pharmacokinetic analysis will be collected from approximately 10-12 evaluable subjects received the combination treatment arm at selected sites. This will enable assessment of drug-drug interactions.

Follow-up Phase

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

A 28(90)-day follow-up visit will be conducted 28(90) (±3) days following the last dose of CC-486 (durvalumab) or during the final treatment phase study visit (whichever date is later) for assessment of the safety-related parameters.

Subjects in follow-up will then be contacted every 3 months from the date of the 28(90)-day follow up visit for CC-486 (durvalumab) until death, loss-to follow-up, withdrawal of consent to further follow-up, or study closure to collect information related to survival, subsequent MDS-related therapies, and disease progression to AML. This will continue until the last active subject completes approximately 12 months of treatment and/or follow-up unless additional follow-up is needed to evaluate time-to-event endpoints. Follow-up contacts will routinely be conducted by telephone unless special circumstances exist.

Study Closure

The study is expected to close when the last subject completes approximately 12 months of treatment and/or follow-up, unless additional follow-up is needed to analyze time-to-event endpoints.

4.2. Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint of this study is the overall rate of objective response (ORR) to treatment with CC-486 as the monotherapy and treatment with CC-486 and durvalumab as combination therapy. The ORR is defined as the proportion of subjects achieving an objective response (HI, PR, CR, or marrow CR) based on modified International Working Group (IWG) 2006 criteria.

4.2.2 Secondary Endpoint(s)

The secondary endpoints of this study are:

- Overall survival;
- Time to onset of responses;
- Duration of responses;
- Progression free survival (time to disease progression or death from any cause);
- Proportion of subjects with progressive disease at baseline achieving Stable Disease, as well as time to achieving stable disease and duration of stable disease;
- The proportion of subjects progressing to AML and time to AML progression;
- Safety and tolerability (type, frequency, severity of AEs and relationship of AEs to CC-486 and/or durvalumab; monitoring for disease progression to AML, as well as immune- and infusion-type reactions);

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- Serum/plasma PK parameters for durvalumab and CC-486, such as maximum observed concentration (Cmax), area under the concentration-time curve (AUC), time to maximum concentration (Tmax), terminal half-life ($t_{1/2}$), clearance (CL/F) and volume of distribution (Vz/F).

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4.3. Sample Size

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

For each cohort, the null hypothesis of the response rate ($H_0 : p \leq 0.125$) will be tested against the alternative hypothesis of the response rate ($H_1 : p \geq 0.27$) with a type I error rate of 10% and 80% power. During the first stage, 16 subjects will be accrued. If there are 2 or fewer responses in these 16 subjects, the cohort will be stopped, and no further recruitment will be needed. Otherwise, 25 additional subjects will be accrued for a total of 41 subjects per cohort. If 8 or more responses are observed in these 41 subjects, the null hypothesis will be rejected.

For each cohort, in addition to the evaluation of treatment responses based on objective response criteria, the quality of responses will also be considered for the decision whether to continue the cohort to the second stage of the study. *Quality of response* will be assessed based on the

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magnitude of hematologic and biologic responses observed in individual subjects, with special consideration for response duration.

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5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the program source (e.g., SAS program name, including the path, that generates the output) and data extraction date (e.g., the database lock date, run date). The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listing will display all the relative values supporting corresponding tables and figures.

Descriptive summaries for continuous data will include the following statistics: N, mean, standard deviation (SD), minimum, median, and maximum, unless specified otherwise. Categorical summaries for discrete data will include the frequency (count) and percentage at each discrete value (category), unless specified otherwise.

5.1.1. Calculation Using dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study medication) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication (dstart) plus 1 day.
    - The generalized calculation algorithm for relative day is defined as:
        a. study day = [(target date – dstart) + 1], if (target date >= dstart).
        b. study day = [(target date – dstart)], if (target date < dstart).
    - Note: Study Day 1 is the first day of treatment of study drug. Negative study days indicate the observations were obtained before the first dose of study drug.
    - Partial date for the first study drug dosing will be imputed according to the criterion in Appendix A of section 14.1. All effort should be tried to avoid incomplete start date of study drug.
- Age (in years) is defined as: [Age = date of consent – date of birth + 1]/365.25 with rounding.
    - Calculation of age should base on the dates in clinical database, otherwise, the calculation will base on dates from CRF or IVRS.

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- Partial birth date will be imputed as follows: impute missing day as 15th of the month; impute missing month as July. If birth year is missing, age will be recorded as missing.

- Algorithm to convert DAYS to WEEKS: WEEKS = DAYS /7.
- Algorithm to convert DAYS to MONTHS: MONTHS = DAYS /30.4167.

5.1.2. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each patient. The start date of the first cycle will be the date when the subject receives the first dose of study drug. Once the start date is calculated, the end date of each cycle is calculated as the day before the start date of the following cycle. For the last cycle, the end date will be calculated as the start date plus prescribed cycle length, or the death date, whichever is earlier. The cycle number will be calculated based on the cycle window set by their start and end dates.

5.2. Analysis Populations

5.2.1. Intent-to-Treat Population

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

5.2.2. Modified Intent-to-Treat Population

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

5.2.3. Safety Population

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

5.2.4. Evaluable Population

The evaluable population includes all ITT subjects who have at least one post-baseline efficacy assessment performed, experienced no major protocol deviations during the study, and have received a minimum of one cycle of treatment are considered to be in the evaluable population.

5.2.5. PK Population

The PK Population includes all subjects who receive at least one dose of study treatment and have at least one measureable plasma/serum exposure. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of the PK, a decision will be made on a case-by-case basis as to the inclusion of his PK data in the statistical analysis.

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5.2.6. Immunogenicity Population

The immunogenicity Population includes all subjects who receive at least one dose of durvalumab and have at least one measureable PK and/or ADA concentration. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of the PK and/or ADA, a decision will be made on a case-by-case basis as to the inclusion in the analysis.

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6. SUBJECT DISPOSITION

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation from study as stated in the study CRF) will be summarized using frequency and percentage for both cohort and follow-up phases.

This will be provided for both ITT and Safety populations. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations. The details will be provided in the study Tables and Listings.

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7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Data on the demographics and baseline clinical characteristics will be summarized for the Safety population, as well as the ITT. Summary for mITT population will be presented only if there is a substantial difference between ITT and mITT populations.

7.1. Demographics

Demographic characteristics consist of age, gender, race, ethnicity, etc., will be summarized for the ITT population and safety population. Age is defined as the integer part of (informed consent date – birth date + 1)/365.25.

7.2. Baseline Clinical Characteristics

Baseline values are defined as the last assessment of a particular parameter (e.g., vital signs, weight, or laboratory assessments) prior to administration of the first dose of IP in the treatment phase of the study, unless noted otherwise for a particular assessment. In most cases, baseline assessments are those performed before dosing on Day 1 of Cycle 1. When there are retested values, the retest values will be used for the analysis.

Data collected in the CRF, including medical history, prior treatments, disease diagnosis, etc., will be summarized using frequency tabulations by system organ class and preferred term.

A similar summary will be generated for the currently active abnormalities only, per body system. Individual subject listings will be provided to support the tables.

The following baseline of clinical characteristics will also be summarized:

- The WHO classification, IPSS classification, and FAB classification of MDS.
- The Eastern Cooperative Oncology Group (ECOG) performance status, and time since initial diagnosis of MDS, which is defined as the number of months from the date of initial diagnosis to the date of informed consent.
- The MDS diagnosis classification at study entry by WHO, IPSS, and FAB criteria, and ECOG performance status, will be summarized categorically. Time since initial diagnosis will be summarized descriptively.

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7.3. Medical History

- Medical history data, including any prior or concomitant diseases and the status of diagnosis if available, will be summarized using frequency tabulations by system organ class and preferred term according to (MedDRA) version 19, or higher.

7.4. Prior MDS Treatment

- A frequency table by Anatomical Therapeutic Chemical (ATC) class and preferred name will be provided according to the coding scheme of the latest version of WHO drug dictionary for all prior treatments of MDS recorded on the CRF, which includes all medications taken for any indication within the 4 weeks (28 days) prior to the first dose of IP. The start date and end date of the treatment if available, the dose and frequency will also be summarized.

7.5. RBC and Platelet Transfusion History

- Documentation of all red blood cell and platelet transfusions received by the subject within 8 weeks (56 days) prior to the first dose of IP will be reported in a listing if recorded on the appropriate CRF. The transfusion data may include the type of transfusion, number of units, reason for, and date of transfusion.

7.6. Pregnancy

- A by-subject listing of status of childbearing potential, pregnancy tests and results as well as menstrual cycles regularity, will be provided for all female patients of childbearing potential if recorded in CRF. For female patients without childbearing potential, the status of hysterectomy, the status of bilateral oophorectomy, and the status of consecutive naturally post-menopausal will also be reported.

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8. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Following variables regarding the extent of study drug exposure are defined and will be summarized.

- ***Treatment Duration:***
    - Definition: (study treatment end date – first study drug start date + 1)/30.4167.
    - Descriptive summary statistics will be provided. An additional table will be created for all treated subjects, displaying number of subjects by cycle. A by-subject listing of all exposure information collected on the CRF will be provided.
- ***Number of Treatment Cycles***:
    - Descriptive summary statistics will be provided for safety population.
- ***Duration of exposure:***
    - Definition: total number of days on the study drug during the treatment period (excluding the periods of dose break per protocol or dose interruptions).
    - Descriptive summary statistics will be provided for safety population.
- ***Average Length of Cycle:***
    - Definition: the number of days on treatment divided by the number of cycles.
    - Descriptive summary statistics will be provided for safety population.
- ***Average Number of Days Dosed Per Cycle:***
    - Definition: the number of days a subject is dosed divided by the number of cycles the subject had.
    - Descriptive summary statistics will be provided for safety population.
- ***Cumulative Dose:***
    - Definition: the sum of all doses taken during the treatment period (in milligrams).
    - Descriptive summary statistics will be provided for safety population by cohort and overall.
- ***Average Daily Dose:***
    - Definition: the cumulative dose of the study drug divided by the number of days dosed (received a non-zero dose).
    - Descriptive summary statistics will be provided for safety population.
- ***Dose Intensity:***

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- Definition: the cumulative dose of the study drug divided by treatment duration of the study drug.
- Descriptive summary statistics will be provided for safety population.

- ***Dose Modification:***
  - Descriptive summary statistics will be provided for safety population, including
    - subjects who have at least one dose reduction/interruption,
    - time to first dose reduction/interruption,
    - first dose reduction/interruption due to AE,
    - duration of first dose reduction/interruption due to AE.

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9. PRIOR/CONCOMITANT MEDICATIONS AND PROCEDURES

Prior medications are defined as medications that were started before the date of first dose of IP (whether or not ended before the date of first dose). Prior medications that continue into study treatment period will be also reported as concomitant medication. Prior medications will be coded in the latest version of the WHO drug dictionary. Medication not in the WHO drug dictionary will be classified as "Not Coded" in the analysis. A frequency table by Anatomical Therapeutic Chemical (ATC) class and preferred term will be provided. A listing of prior medications documented on the CRF will also be provided. All prior and concomitant medications (prescription and non-prescription), treatments, and therapies taken from 84 days (12 weeks) prior to the first dose of IP, up to 28 days after the last dose of IP or up to the last study visit, whichever date is later, will be analyzed. All prior treatments for MDS, including ESAs, thrombopoiesis-stimulating agents (TSAs), iron-chelating agents, chemotherapy, cytotoxic therapy, investigational agents, or other medications considered supportive care for MDS should be recorded on the respective CRF(s) regardless of discontinuation date of treatment.

Concomitant medication is defined as all medications taken from the date of first dose until 28 days after the last dose of IP or until the last study visit, whichever period is longer. Concomitant medications will be coded in the latest version of the WHO drug dictionary. Medication not in the WHO drug dictionary will be classified as "Not Coded" in the analysis. The Anatomical Therapeutic Chemical (ATC) coding scheme of the WHO will be used to group medications into relevant categories. A frequency table by ATC class and preferred term will be provided. All concomitant medications documented on the CRF will be listed for the safety population.

The total number of prior and concomitant medications and the number and percentages of patients with at least one prior and one concomitant medication will be summarized. The number and percentages of all prior and concomitant medications will be summarized and listed by drug class and preferred term.

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10. EFFICACY ANALYSIS

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

10.1. Primary Efficacy Analysis

The primary assessment of efficacy will be the overall rate of response (defined as CR, PR, or mCR), and HI as determined using the modified IWG 2006 response criteria for MDS.

Hematologic response (CR, PR, mCR, and HI) will be determined by investigator assessment and responses will also be derived, summarized and analyzed separately. The percentage of these responses will be estimated separately, and the corresponding 95% confidence interval will also be provided. The percentage of subjects with other response outcomes of stable disease, failure, relapse after CR or PR, and disease progression will also be presented.

- ***Hematologic Response*** (including CR, PR, mCR, SD, Failure, Relapse after CR or PR, and Cytogenetic Response) is defined according to modified IWG 2006 criteria. Subjects will be classified according to their best response achieved during treatment for the response categories of CR, PR, mCR, SD, and failure. Only subjects who achieve CR or PR will be included in the Relapse after CR or PR category. Subjects will be evaluated for cytogenetic response regardless of their response status in other categories. Hematologic response will be presented descriptively using counts and percentages.
- ***Cytogenetic Response*** Subjects will be classified as having a complete or partial response based on the best response achieved during treatment. Responses will be presented descriptively using counts and percentages.
- The response rates at the end of Stage 2 and the associated 90% confidence interval will be estimated for each cohort which completes Stage 2. Similar estimates for Stage 1 will be provided for any cohort which does not continue to Stage 2.
- The response rates at the end of Stage 2 will be compared between cohorts of SD and PD subjects (if both cohorts finished Stage 2) using the relative risk ratio or other appropriate methods. Specifically, if relative risk method is used, the ratio of response rates for both cohorts and the associated 90% confidence interval will be estimated.

10.2. Secondary Efficacy Analyses

10.2.1. Overall Survival

- Overall survival (OS), time to death from any cause, will be calculated using date of first dose and date of death, or date of last follow-up for censored subjects. Time to death from any cause is defined as the time between first dose and death from any cause.
- All subjects will be followed until drop-out, death, or study termination. Drop-out may be due to withdrawal of consent from further data collection or loss to follow-up. Subjects

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who drop-out or are alive at study termination will have their OS times censored at the time of last contact, as appropriate.

- The OS will be estimated using Kaplan-Meier (KM) method.

10.2.2. Time to Onset of Response

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

10.2.3. Duration of Response

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

10.2.4. Progression-free Survival

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

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10.2.5. Stable Disease

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

10.2.6. Disease Progression to AML

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

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11. SAFETY ANALYSIS

The purpose of this section is to define the safety analysis for the study. All summaries of safety data will be conducted using the safety population. Descriptive statistics will be provided by disease cohort and treatment arm.

11.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) of Version 22. Adverse event listings will include the verbatim term and the MedDRA preferred term. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. For any AE not listed in the CTCAE grading system, the intensity of these events will be assessed by the Investigator using a 5-point scale as described in protocol.

If a subject experiences multiple AEs under the same PT (SOC), the subject will be counted only once for that PT (SOC). If a subject experiences the same AE more than once with a different intensity grade, the event with the highest grade will be tabulated in "by grade" tables. In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing" and will not be imputed.

Treatment emergent adverse events (TEAEs) are defined as AEs occurring or worsening on or after the date of the first dose of the study treatment (CC-486 or durvalumab) and within 28 days after last dose of CC-486 or 90 days after last dose of durvalumab. A treatment-related TEAE is defined as a TEAE where the causal relationship was assessed by the investigator as "Suspected". If the relationship between a TEAE and a study drug is missing, the TEAE will be considered to be related to the study treatment.

Summary tables for the incidence of TEAEs will be summarized by disease cohort, treatment arm, SOC, and PT within SOC. They will be sorted by alphabetically order of SOC and PT, and then sorted by decreasing frequencies, unless otherwise specified. Following tables will be generated:

- TEAEs;
- TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab;
- TEAEs of CTCAE grade 3 or 4;
- TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab with CTCAE grade 3 or 4;
- TEAEs with death outcome;
- TEAEs with death outcome related to CC-486 only, durvalumab only, or CC-486 or durvalumab;

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- Serious TEAEs;
- Serious TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab;
- TEAEs leading to discontinuation of CC-486 only, durvalumab only, or CC-486 or durvalumab;
- TEAEs leading to dose reduction of CC-486;
- TEAEs leading to dose interruption of CC-486 only, durvalumab only, or CC-486 or durvalumab;
- TEAEs leading to infusion interruption of durvalumab.

As well as

- TEAEs by cycle of onset as well as the safety run-in period;
- TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab, by cycle of onset;
- TEAEs by maximum CTCAE grade;
- TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab, by maximum CTCAE grade;
- Common (>=10%) TEAEs;
- Common (>=10%) TEAEs related to CC-486 only, durvalumab only, or CC-486 or durvalumab;
- By age category: <65, 65-74, ≥75;
- By gender.

All deaths, on treatment deaths, off treatment deaths and causes of death will be summarized from the Death form in the CRF. Deaths within or 28 days after last dose of CC-486 or 90 days after the last dose of durvalumab will be summarized separately.

Individual subject listing of AEs will be presented. In addition, the following listings will be provided:

- Listing of SAE;
- Listing of TEAEs leading to permanent withdrawal of any study drug
- Listing of all TEAEs with outcome of death
- Listing of all subjects who died

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CCI [redacted]

The AEs CCI [redacted] The following TEAEs CCI [redacted]

- Myelosuppression (neutropenia, thrombocytopenia, anemia, general myelosuppression)
- Gastrointestinal disorders
- Hemorrhagic events
- Infections
- Renal failure
- Hepatic failure
- Ischemic colitis
- Interstitial lung disease
- Cardiac events (cardiac failure, cardiac arrhythmias, myocardial infarction)
- Anxiety, Confusional state, Insomnia
- Other psychiatric disorders
- Tumour lysis syndrome

Although not determined as an important risk in the Vidaza RMP, gastrointestinal events as defined by System Organ Class Gastrointestinal disorders will also be summarized as an adverse event of special interest for this study.

For durvalumab, following are the AESIs for Ongoing Surveillance Activities based on pre-defined search criteria as provided by Astrazeneca/MedImmune:

- Diarrhoea
- Colitis
- Intestinal perforations
- Pneumonitis
- Hepatitis
- Hepatic laboratory parameters reported as AEs
- Adrenal insufficiency
- Type 1 diabetes mellitus
- Hypophysitis
- Thyroiditis

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- Hyperthyroidism
- Thyroid laboratory parameters reported as AEs (increased thyroid activity))
- Hypothyroidism
- Thyroid laboratory parameters reported as AEs (decreased thyroid activity))
- Rash
- Dermatitis
- Nephritis
- Renal laboratory investigations reported as AEs
- Pancreatitis
- Pancreatic laboratory investigations reported as AEs
- Myocarditis
- Myositis
- Myasthenia gravis
- Guillain-Barré syndrome
- Other rare/miscellaneous
- Hypersensitivity / Anaphylactic reactions
- Infusion related reaction

After review of the data, there may be other AEs of special interest identified. For summaries based on selected MedDRA preferred terms, the final selection of inclusive preferred terms will be performed based on review of final data to ensure all relevant terms are captured. Summary table will be provided for all TEAEs included in the above-mentioned AEs of special interest.

- All TEAEs
- TEAEs of Grade 3 or 4
- Serious TEAEs
- TEAEs leading to study drug withdrawal
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug dose interruption
- TEAEs leading to death

The incidence rate per 100 person-years will also be derived for each AESI.

11.2. Clinical Laboratory Evaluations

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Clinical laboratory test results in SI units will be summarized descriptively and will include a display of change from baseline to each post-dose scheduled time point. Baseline values for all lab tests will be the last non-missing value on or before date of first treatment.

Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and non-hematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized. Clinical laboratory values will be presented using the reported units.

11.3. Vital Sign Measurements

Vital sign measurements reported in CRF and physical examinations will be summarized descriptively, and listed for each subject at baseline and each visit after, and change from baseline will be summarized. A listing of vital signs will be provided.

11.4. ECOG Performance Status

ECOG performance will be summarized categorically with a shift from baseline by cycle, end of study and maximum shift by treatment. Individual subject data will be listed. The last ECOG performance score prior to and including the date of the first dose of study drug will be used as the baseline value.

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

Bone marrow and peripheral blood samples will be collected at screening and following every 2 cycles of treatment during the first 6 treatment cycles (i.e., Cycle Day 28 [± 14 days]). Subjects who continue beyond Cycle 6 will undergo bone marrow examination following every 3 treatment cycles or when necessary to confirm suspected hematologic response or disease progression, and again upon treatment discontinuation. The data collected in CRF will be summarized in table and listing.

11.6. Electrocardiogram

An electrocardiograms (ECG) will be conducted and analyzed locally at screening and at treatment discontinuation by the local laboratory. The ECG is to 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 will report abnormal finding(s) on the respective CRF. If the ECG is abnormal, the investigator should consult a cardiologist if deemed appropriate. The ECG data from CRF will be summarized.

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12. INTERIM ANALYSIS

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

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13. PHARMACOKINECTIC ANALYSES

The following PK analyses were planned but not conducted in the combination arm which was stopped since the optimal combination dose could not be determined. Only a few subjects were enrolled in the combination arm who agreed to PK sample collection and due to the limited samples collected, the PK TLGs will not be generated.

13.1 CC-486

13.1.1 Plasma concentrations

By-subject listing of pharmacokinetic blood sample collection times as well as derived sampling time deviations will be provided. CC-486 plasma concentrations will be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation).

Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Missing concentrations and concentrations from blood samples collected more than ± 10% of nominal time will be omitted from the calculation of descriptive statistics.

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

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

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

Actual sampling times will be used in the calculations of pharmacokinetic parameters that will be derived using non-compartmental (NCA) methods with Phoenix™ WinNonlin® Professional

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Version 6.4, or higher, (Pharsight®, a Certara™ company, St. Louis, Missouri). Graphics may be prepared with SAS Version 9.3, or higher; or Excel 2007, or higher; Phoenix™ WinNonlin® Professional 6.4, or higher.

13.1.2 PK Parameter

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

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

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

λ_z	Apparent terminal rate constant, calculated by linear regression of the terminal portion of the log-concentration versus time curve in plasma. Visual assessment will be used to identify the terminal linear phase of the concentration versus time profile. A minimum of three data points will be used for calculation. λz will not be estimated if the terminal phase of the log-concentration versus time profile does not exhibit a linear decline phase, or if the regression coefficient < 0.8.
λ_z lower	Lower limit of time (h) included in the calculation of λ_z.
λ_z N	Number of data points used in the calculation of λ_z.
λ_z upper	Upper limit of time (h) included in the calculation of λ_z.
Rsq	Regression coefficient for calculation of λ_z.
$\%AUC_{extrap}$	Percentage of $AUC_{0-\infty}$ due to extrapolation from the last quantifiable time point to infinity.

13.1.3 PK Analyses

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

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

CCI [redacted]

13.2 Durvalumab

13.2.1 Plasma concentrations

By-subject listing of pharmacokinetic blood sample collection times as well as derived sampling time deviations will be provided. Durvalumab serum concentrations will be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation).

Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Missing concentrations and concentrations from blood

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samples collected more than ± 10% of nominal time will be omitted from the calculation of descriptive statistics.

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

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

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

Actual sampling times will be used in the calculations of pharmacokinetic parameters that will be derived using non-compartmental (NCA) methods with Phoenix™ WinNonlin® Professional Version 6.4, or higher, (Pharsight®, a Certara™ company, St. Louis, Missouri). Graphics may be prepared with SAS Version 9.3, or higher; or Excel 2007, or higher; Phoenix™ WinNonlin® Professional 6.4, or higher.

13.2.2 PK Parameter

The following PK parameters will be calculated for durvalumab on Cycle 1:

$AUC_{0-\infty}$ Area under the serum concentration-time curve from Time 0 extrapolated to infinity, calculated as $[AUC_{0-t} + Ct/\lambda_z]$. C_t is the last quantifiable concentration. No AUC extrapolation will be performed with unreliable λ_z. If $\%AUC_{extrap}$ is ≥25%, $AUC_{0-\infty}$ will not be reported.

AUC_{0-t} Area under the serum concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

C_{max} Maximum observed serum concentration, obtained directly from the observed concentration versus time data.

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T_{max}	Time to C_{max}, obtained directly from the observed concentration versus time data.
$t_{1/2}$	Terminal phase half-life in serum, calculated as $[(\ln 2)/\lambda_z]$. $t_{1/2}$ will only be calculated when a reliable estimate for λ_z can be obtained.
CL	Total clearance, calculated as $[Dose/AUC_{0-\infty}]$.
Vz	Volume of distribution, calculated as $[(CL)/\lambda_z]$.

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

λ_z	Apparent terminal rate constant, calculated by linear regression of the terminal portion of the log-concentration versus time curve in serum. Visual assessment will be used to identify the terminal linear phase of the concentration versus time profile. A minimum of three data points will be used for calculation. λz will not be estimated if the terminal phase of the log-concentration versus time profile does not exhibit a linear decline phase, or if the regression coefficient < 0.8.
λ_z lower	Lower limit of time (h) included in the calculation of λ_z.
λ_z N	Number of data points used in the calculation of λ_z.
λ_z upper	Upper limit of time (h) included in the calculation of λ_z.
Rsq	Regression coefficient for calculation of λ_z.
$\%AUC_{extrap}$	Percentage of $AUC_{0-\infty}$ due to extrapolation from the last quantifiable time point to infinity.

The following PK parameters will be calculated for durvalumab on Cycle 2:

AUC_{0-t}	Area under the serum concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.
C_{max}	Maximum observed serum concentration obtained directly from the observed concentration versus time data.
T_{max}	Time to C_{max}, obtained directly from the observed concentration versus time data.

Note: only the 3 PK parameters listed above will be calculated as durvalumab is expected to not be at BLQ level at the start of Cycle 2.

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13.2.3 PK Analyses

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

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

CCI [redacted]

13.3 Immunogenicity

From all subjects dosed with durvalumab, 6 PK and 6 immunogenicity predose samples (Cycle 1, 2, 4, 6, 10, and 14 Day 1), Anti-Drug Antibody (ADA), should have been collected.

By-subject listing of pharmacokinetic and ADA blood sample collection times will be provided. Durvalumab serum concentrations and ADA will be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation).

[redacted] CCI [redacted].

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14 REFERENCES

1. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials. 1989; 10:1-10.

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15 APPENDICES

15.1 Appendix A: Date Imputation Guideline

15.1.1 Impute Missing AE start day and month [namely, dd & mm in dd-mm-yyyy are missing]

- If yyyy(AE) = yyyy(1st day of study medication), then
  - dd(AE) = dd(1st day of study medication)
  - mm(AE) = mm(1st day of study medication)
- If yyyy(AE) < yyyy(1st day of study medication), then
  - dd(AE) = 31
  - mm(AE) = December
- If yyyy(AE) > yyyy(1st day of study medication), then
  - dd(AE) = 1
  - mm(AE) = January

14.1.2 Missing AE start month only [namely, mm in dd-mm-yyyy is missing]

- If yyyy(AE) = yyyy(1st day of study medication), then
  - mm(AE) = mm(1st day of study medication)
- If yyyy(AE) < yyyy(1st day of study medication), then
  - mm(AE) = December
- If yyyy(AE) > yyyy(1st day of study medication), then
  - mm(AE) = January

14.1.3 Missing AE start day only [namely, dd in dd-mm-yyyy is missing]

- If yyyy(AE) = yyyy(1st day of study medication), then
  - If mm(AE) = mm(1st day of study medication), then
    - dd(AE) = dd(1st day of study medication)
  - If mm(AE) > mm(1st day of study medication), then
    - dd(AE) = 1
  - If mm(AE) < mm(1st day of study medication), then

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        - dd(AE) = last day of mm(AE)
- If yyyy(AE) < yyyy(1st day of study medication), then
    - If AE stop date exists and is complete, then
        - dd(AE) = dd(AE stop);
    - if AE stop date does not exist or is incomplete, then
        - dd(AE) = last day of mm(AE)
- If yyyy(AE) > yyyy(1st day of study medication), then
    - dd(AE) = first day of mm(AE)

14.2.1 Missing AE stop day and month [namely, dd & mm in dd-mm-yyyy are missing]

- If yyyy(AE) = yyyy(last day of study medication), then
    - dd(AE) = dd(last day of study medication)
    - mm(AE) = mm(last day of study medication)
- If yyyy(AE) < yyyy(last day of study medication), then
    - dd(AE) = 31
    - mm(AE) = December
- If yyyy(AE) > yyyy(last day of study medication), then
    - dd(AE) = 1
    - mm(AE) = January

14.2.2 Missing AE stop month only [namely, mm in dd-mm-yyyy is missing]

- If yyyy(AE) = yyyy(last day of study medication), then
    - mm(AE) = mm(last day of study medication)
- If yyyy(AE) < yyyy(last day of study medication), then
    - mm(AE) = December
- If yyyy(AE) > yyyy(last day of study medication), then
    - mm(AE) = January

14.2.3 Missing AE stop day only [namely, dd in dd-mm-yyyy is missing]

- If yyyy(AE) = yyyy(last day of study medication), then
    - If mm(AE) = mm(last day of study medication), then

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        - dd(AE) = dd(last day of study medication)
    - If mm(AE) > mm(last day of study medication), then
        - If AE start date exists and is complete, then
            - dd(AE) = dd(AE start);
        - if AE start date does not exist or is incomplete, then
            - dd(AE) = first day of mm(AE)
    - If mm(AE) < mm(last day of study medication), then
        - dd(AE) = last day of mm(AE)
- If yyyy(AE) < yyyy(last day of study medication), then
    - dd(AE) = last day of mm(AE)
- If yyyy(AE) > yyyy(last day of study medication), then
    - If AE start date exists and is complete, then
        - dd(AE) = dd(AE start);
    - if AE stop date does not exist or is incomplete, then
        - dd(AE) = first day of mm(AE)

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15.2 Appendix B: Myelodysplastic Syndromes World Health Organization Classification System

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

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		< 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rods + and/or 5% to 19% blasts in the blood.

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

Sources:

1. Brunning RD, Bennett JM, Flandrin G, Matutes E, Head D, Vardiman JW, et al. Pathology and genetics of tumors of hematopoietic and lympoid tissues. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumors. Lyon (France). IARC Press, 2001:63-73.
2. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute myeloid leukemia: rationale and important changes. Blood 2009; 114(5):937-51.

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15.3 Appendix C: International Prognostic Scoring System Score

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

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

[b] Defined as: Hemoglobin < 100 g/L, absolute neutrophil count < 1.5 x 10^9/L, and platelet count < 100 x 10^9/L.

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

Source:

1. 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.

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15.4 Appendix D: ECOG Performance Status

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

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

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15.5 Appendix E: Hematologic Response According to the IWG Criteria for MDS

Modified Hematologic Response According to IWG Criteria for MDS	
Category	**Response criteria (responses must last at least 4 weeks)**
Complete Remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] Hgb ≥ 11 g/dL Platelets ≥ 100 X 10^9/L Neutrophils ≥ 1.0 X 10^9/L[b] Blasts 0%
Partial Remission (PR)	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subcancer than pretreatment
Relapse After CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete - Disappearance of the chromosomal abnormality without appearance of new ones Partial - At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence

KEY: CR = complete remission; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PFS = progression free survival; PR = partial remission

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

[b] Modification to IWG response criteria.

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

Notes: Subjects with CMML will be assessed for response using the IWG criteria for MDS. Deletions to IWG response criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

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

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Modified Hematologic Improvement According to IWG Criteria	
Hematologic improvement[a]	**Response criteria (responses must last at least 8 week)[b]**
Erythroid Response (HI-E) (pretreatment, <11 g/dL)	Hemoglobin 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 hemoglobin of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation[b]
Platelet Response (HI-P) (pretreatment, <100 X 10^9/L)	Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%[b]
Neutrophil Response (HI-N) (pretreatment, <1.0 X 10^9/L)	At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HI[c]	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in hemoglobin by ≥ 1.5 g/dL Transfusion dependence

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

[a] Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).

[b] Modification to IWG response criteria.

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

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

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

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