DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

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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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Durvalumab (MEDI4736) + Azacitidine

PROTOCOL NUMBER: MEDI4736-MDS-001

DATE DRAFTED: 23 Oct 2017

Prepared by:

CCI [redacted]

On behalf of Celgene Corporation

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SAP TITLE	MEDI4736-MDS-001 Statistical Analysis Plan
SAP VERSION, DATE	Final Version, 23 Oct 2017
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INVESTIGATIONAL PRODUCT	Durvalumab (MEDI4736)
PROTOCOL NUMBER	MEDI4736-MDS-001
PROTOCOL VERSION, DATE	Amendment N°1, 27 Mar 2017
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Study Statistician Signature Printed Name	PPD Date PPD
Statistical Therapeutic Area Head Signature Printed Name	PPD Date PPD
Lead Clinical Research Physician / Clinical Research Physician Signature Printed Name	PPD Date PPD
Lead Product Safety Physician Signature Printed Name	PPD Date PPD

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
CCI [redacted]	[redacted]
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical therapeutical chemical
BM	Bone marrow
BMA	Bone marrow aspirate
BMI	Body mass index
BSA	Body surface area
CrCL	Creatinine clearance
CyCR	Cytogenetic response
CI	Confidence interval
CKD	chronic kidney disease
CR	Complete response/Complete remission
CRc	Cytogenetic complete remission
CRi	Complete remission with incomplete blood recovery
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy evaluable

Abbreviation or Specialist Term	Explanation
CCI [redacted]	[redacted]
EOT	End of treatment
Hgb	Hemoglobin
HI	Hematological improvement
HI-E	Hematological improvement – erythroid
HI-N	Hematological improvement – neutrophil
HI-P	Hematological improvement – platelet
CCI [redacted]	[redacted]
[redacted]	[redacted]
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
IP	Investigational product
IPSS-R	Revised - International prognostic scoring system
IRT	Interactive Response Technology
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive voice response system
IWG	International working group
KM	Kaplan-Meier
mCR	Marrow complete remission
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndromes
ORR	Overall response rate
OS	Overall survival
Pd	Pharmacodynamics
PD	Progressive disease
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PFS	Progression-free survival
PK	Pharmacokinetics

Abbreviation or Specialist Term	Explanation
PR	Partial response/remission
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
RMP	Risk management plan
RFS	Relapse free survival
sc	Steering committee
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SBP	Systolic blood pressure
SD	Stable disease
CCI	[redacted]
SMQ	Standardized MedDRA Query
SOC	System organ class
STD	Standard Deviation
TEAE	Treatment emergent adverse event
TTR	Time to response
WBC	White blood cell
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations to be performed for Celgene's protocol 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 MDS or in elderly (≥ 65 years) AML subjects not eligible for hematopoietic stem cell transplantation (HSCT) (MEDI4736-MDS-001)" which was issued on 17 Nov 2015 and amended on 27 Mar 2017. The SAP contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety.

These analyses include interim analysis, final analysis (after 6 cycles) and additional analysis (after 12 months). Throughout this SAP, the treatment arms will be referred to as subcutaneous azacitidine plus durvalumab and subcutaneous azacitidine alone. The purpose of the SAP is to ensure the credibility of the study findings by prespecifying the statistical approaches to the analyses of study data prior to database lock for the study. This SAP provides a description of the strategy, rationale, and statistical techniques to be used to achieve the objectives of the study.

The SAP will be finalized and signed off prior to the clinical database lock for the interim analysis. All statistical analyses detailed in the SAP will be conducted using SAS® Version 9.3 or higher.

3. OBJECTIVES

Primary objectives

- To evaluate the efficacy of subcutaneous azacitidine in combination with durvalumab as compared to subcutaneous azacitidine alone in the defined study population.

Secondary objectives

- To assess the safety and tolerability of subcutaneous azacitidine in combination with durvalumab as compared to subcutaneous azacitidine alone in the defined study population.
- To assess the pharmacokinetics (PK) of durvalumab when given in combination with subcutaneous azacitidine in the defined study population.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, multicenter, randomized, parallel-group, open-label study evaluating the efficacy and safety of subcutaneous azacitidine either alone or in combination with durvalumab in two separate cohorts. Cohort 1 comprises subjects with previously untreated myelodysplastic syndrome (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), or IPSS-R high or IPSS-R very high risk, who are not eligible for HSCT. Cohort 2 comprises subjects with previously untreated acute myeloid leukemia (AML) (de novo AML with ≥20% blasts) or secondary AML, as per WHO classification, 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)

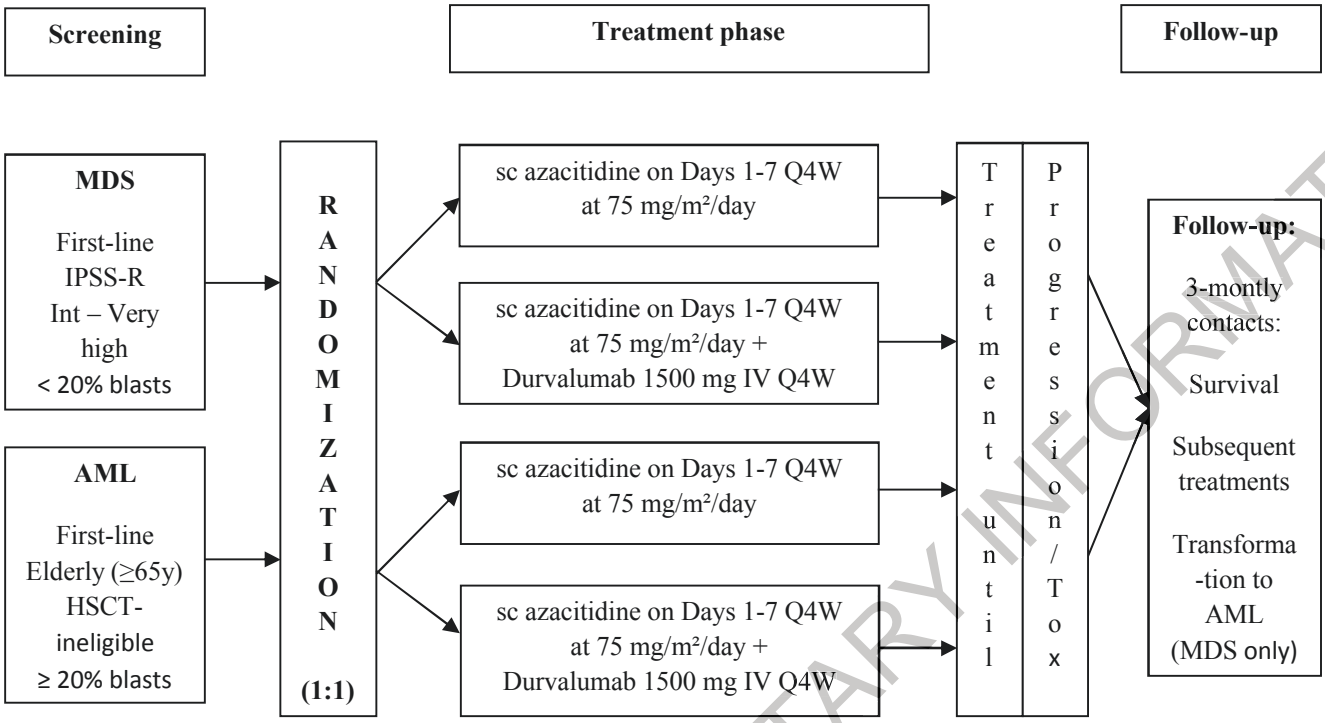
The randomization process will aim to balance prognostic factors between study arms. For both cohorts (MDS and AML), subjects will be randomized and stratified according to their cytogenetic risk:

- Intermediate versus poor for AML (Appendix 17.5),
- Very good, good and intermediate versus poor and very poor for MDS (Appendix 17.4).

The randomized study will be conducted in 2 stages, with an interim analysis for futility purpose for each of the 2 disease cohorts determining whether that cohort proceeds to Stage 2. The interim analysis will be conducted in the MDS cohort when the first 30 subjects have completed 6 cycles of treatment unless they have established an earlier response (CR. mCR, PR or HI) or discontinued due to death or disease progression while the interim analysis in the AML cohort will be conducted when the first 50 subjects have completed 6 cycles of treatment unless they have established an earlier response (CR or CRi) or discontinued due to death or disease progression. Subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the interim analysis.

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 of the protocol. In addition, early safety monitoring meetings will be performed after 6 subjects and after 12 subjects have completed 2 treatment cycles.

Figure 1: Overall Study Design



AML = acute myeloid leukemia; Int = intermediate; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; Q4W = every 4 weeks; sc = subcutaneous.

Study Population

A total of approximately 182 eligible 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 of the protocol, 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 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 of the protocol).

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 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 analyses, whichever is the later date. See Section 3.3 of the protocol.

Study Treatments

Subjects will be randomized 1:1 to receive either:

Treatment Arm A: Subcutaneous azacitidine (75 mg/m^2 daily 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 daily for 7 days Q4W.

Table 2: Study Endpoints

Endpoint	Name	Description
MDS Cohort		
Primary	Overall response rate	Proportion of MDS subjects achieving an overall response (CR, mCR, PR or HI), based on IWG 2006 response criteria (Appendix 17.2).
Secondary	Time to response	Time from randomization to first documented response according to IWG 2006 response criteria (Appendix 17.2).
	Relapse-free survival	Time from the date CR or PR 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 17.2).
	Cytogenetic response (CyCR)	Proportion of subjects achieving complete cytogenetic response or partial cytogenetic response according to IWG 2006 response criteria (Appendix 17.2).
	Progression-free survival (PFS)	Time from randomization to the first documented PD, relapse or death due to any cause, whichever occurs first.
	Duration of response	Duration of response is defined as the time from first response observed (CR, mCR, PR or HI) until relapse, PD or death as defined by the IWG 2006 criteria (Appendix 17.2).
	Time to AML transformation	Time from randomization to AML transformation defined by at least 30% of myeloblasts either in the bone marrow or the peripheral blood.
	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 17.3).
Secondary	Time to response	Time from randomization to first documented response based on modified IWG 2003 response criteria for AML (Appendix 17.3).
	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.
	Complete cytogenetic Response (CyCR)	Proportion of subjects with complete cytogenetic response (CyCR) based on modified IWG 2003 response criteria for AML (Appendix 17.3).

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
	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 17.3) or death due to any cause, whichever occurs first.
	Hematologic Improvement Rate	Proportion of subjects achieving a hematological improvement (HI-N + HI-P + HI-E) according to IWG 2006 response criteria (Appendix 17.2).
Both Cohorts		
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs), and relationship of AEs to study treatment, clinical laboratory evaluations.
	Overall survival (OS)	Time from randomization to death due to any cause.
	One-year survival	The probability of survival at 1 year from randomization.
	PK	Durvalumab concentration.
CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted] = 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; OS = overall survival; PD = progressive disease; CCI [redacted] PK = pharmacokinetics; PR = partial remission.

4.2. Stratification, Randomization, and Blinding

The study will be conducted in 2 stages for each disease cohort (Section 9.3 of the protocol). Subjects will be randomized with 1:1 ratio to receive subcutaneous azacitidine alone 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, intermediate versus poor or very poor for the MDS cohort (Appendix 17.4, IPSS-R Cytogenetic Risk Groups), and intermediate versus poor for the AML cohort (Appendix 17.5).

This study will employ dynamic randomization based on two stratification factors (defined above) to achieve an even treatment balance between (A) Combination and (B) Monotherapy.

Step 1: Determine Primary (Disease Type) and Secondary (Cytogenetic Risk Factor) Stratification Factors

Subjects will first be stratified based on the disease type of either MDS or AML, as the secondary stratification factor variable depends on this information. Once disease type has been identified, the secondary stratification factor of cytogenetic risk factor can be identified. Cytogenetic risk factor options for each disease type are as follows:

- MDS: Very good, good and intermediate vs. Poor and Very Poor
- AML: Intermediate vs. Poor

Step 2: Determine Evaluable Subjects

Only evaluable subjects will be considered when dynamic randomization is performed. Evaluable subjects are those who have been randomized and NOT been marked as replacement eligible via the Replacement Eligibility Review admin module.

Step 3: Determine Set of Ranges

To achieve treatment balance the measure of variability needs to be defined and is a quantitative way to describe the imbalance of patients amongst the treatment arms. Specifically, the measure of variability for this procedure is the Range which is the difference between the number of patients in the treatment arm with the most patients and the number of patients in the treatment arm with the least patients. For example, if treatment A has 4 patients and treatment B has 3 patients, the Range is 1, ie, 4 (maximum) – 3 (minimum). When a new subject is to be randomized, the potential Ranges will be calculated for each possible treatment assignment. This will provide a Set of Ranges that measures the potential imbalance resulting from assigning a patient to the different treatments.

For example, the current enrollment (of evaluable subjects) for the MDS disease type is:

	Treatment A	Treatment B
Total Randomized	6	5
Level/Stratum Balance		
Intermediate	4	3
Poor and Very Poor	2	2

The next subject to be randomized has disease type MDS and is Intermediate cytogenetic risk. First step is to calculate the Set of Ranges for the Intermediate level.

If the subject were to be assigned to treatment A the totals would become 5 and 3 and the intermediate level range would be 2, as calculated by Treatment A – Treatment B = 2.

	Treatment A	Treatment B
Intermediate	5	3

If the subject were to be assigned Treatment B the Range would be 4 – 4 = 0 for the strata.

	Treatment A	Treatment B
Intermediate	4	4

Step 4: Determine the Rank

Continuing with the above example, since Treatment B has the lowest Range, it receives Rank 1 and Rank 2 would be assigned to Treatment A.

Step 5: Determine the Appropriate Cumulative Representation

Using the tables below and considering that in the scenario above, Rank 1 <> Rank 2 we would reference Rank Scenario 4 to determine the appropriate Cumulative probabilities. Ultimately based on this Rank Scenario the probability to randomize the patient to treatment A or B will be 1/1 if there is no difference in Rank (Rank Scenario 1 below). Otherwise, the probability will be 9/1 – with the treatment defined as Rank 1 above receiving the higher probability (Rand Scenario 2 below).

Rank Scenario 1: Rank 1 = Rank 2

Rank	Probability	Decimal Probability	Cumulative Probability
Rank 1	1/2	0.5	0.5
Rank 2	1/2	0.5	1.0

Rank Scenario 2: Rank 1 <> Rank 2

Rank	Probability	Decimal Probability	Cumulative Probability
Rank 1	9/10	0.9	0.9
Rank 2	1/10	0.1	1.0

Step 6: Query the Random Number table

A table is required that contains a sequence of random numbers between 0.0000 and 1.0000. This list should be uniformly distributed. Based on the next unassigned random number on the list. If the number is <= Rank 1 cumulative probability, then the treatment in Rank 1 gets the assignment. If the number is > Rank 1 cumulative probability then the treatment in Rank 2 gets the assignment.

Blinding : not applicable for this study.

4.3. Sample Size

A total of approximately 182 eligible subjects will be enrolled in the study, with a total of 72 subjects in the MDS cohort and 110 subjects in the AML cohort.

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).

4.3.1. MDS Cohort

Sekeres et al (Sekeres, 2014) demonstrated that treating subjects with higher-risk MDS resulted in an overall response rate (ORR) (complete remission [CR], marrow complete remission [mCR], partial remission [PR], hematological improvement [HI]) of 36% after four cycles of azacitidine alone. 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 (CR. mCR, PR or HI) or discontinued due to death or disease progression. Subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the interim analysis.

The MDS cohort will continue to enroll a total of 72 MDS subjects if one of the below conditions is met at the interim analysis:

- If the ORR (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 clinically 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 data monitoring committee (DMC) will review the data at the time of interim analysis and will provide recommendation/advice to Celgene.

4.3.2. AML Cohort

Studies conducted by Dombret et al and Fenaux et al (Dombret, 2015; Fenaux, 2010) showed a response (CR + complete remission with incomplete blood recovery [CRi]) rate of 25% in AML subjects treated with azacitidine. Assuming a treatment effect of 100% relative improvement of CR and CRi (from 25% to 50% absolute CR and CRi 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 (CR or CRi) or discontinued due to death or disease progression. Subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the interim analysis.

The AML cohort will continue to enroll a total of 110 AML subjects if one of the below conditions is met at the interim analysis:

- If the ORR (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.

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 following:

- Program source (eg, SAS program name, including the path, that generates the output) and
- Data extraction date (eg, 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 listings will display all the relative values supporting corresponding table and figure.

5.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9 datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, bone marrow aspirates or biopsies, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in the case report form (CRF) data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 17.1 (eg, for duration or cycle assignment etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.

- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules (see Section 5.1.2 below).

Dates recorded in comment fields will not be imputed or reported in any specific format.

5.1.2. Calculations Using Dates

Calculations using dates (eg, 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 plus 1 day. The generalized calculation algorithm for relative day calculations will be [date of interest – treatment start date + (date of interest >= treatment start date)]. This calculation will result in dates prior to the treatment start date being presented as negative days, and those occurring on or after the treatment start date as Day 1 or later, ie, there will be no Day 0. Note: Partial date for the first study drug is not imputed in general. All effort should be made to avoid incomplete study drug start date.
- Age (expressed in days) is calculated:

  AGE = DATE of informed consent – DATE of BIRTH + 1. In practice, age will be transformed into years by dividing the difference by 365.25 days, then truncating.

  - Using calculated age from the clinical database is preferred. When not available, the calculated/reported age from the CRFs or interactive voice response system (IVRS) may be used
  - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set age as missing if missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS / 7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS / 30.4375.

5.1.3. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the first cycle will be the date when the subject receives any dose of study drug. First dose date of Durvalumab infusion or azacitidine injection in each cycle will be considered as the start of the cycle.

Once the start dates, eg, S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, ie, $E_i = S_{i+1} - 1$. The last cycle in the treatment

phase is defined as the cycle with the last dose of any study drug. For the last cycle, the end date will be the last dose date plus 28 days or the death date, whichever is earlier.

The cycle number for each date of interest, eg, AE or lab, will be calculated based on the cycle window set by their start and end dates. If a date is on or after Si and before Si+1, the corresponding cycle number will be i.

5.1.4. Descriptive Statistics

By default, descriptive statistics for continuous variable include: n, Mean, Standard Deviation (STD), Q1 and Q3, Median, Minimum (Min), and Maximum (Max). Unless specified in the actual table shells, the mean, median, Q1 and Q3 should be displayed to the one more decimal place than the original data (derived analysis data). Standard deviation should be displayed to the two more decimal places than the original data (derived analysis data). The minimum and maximum should be displayed to the same number of decimal places as the original data.

5.2. Analysis Populations

5.2.1. 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.

5.2.2. 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 assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the EE population.

An earlier response is defined as CR, mCR, PR or HI before the end of cycle 6 for the MDS cohort or CR and CRi before the end of cycle 6 for the AML cohort.

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

5.2.3. Safety Population

The Safety Population will include all subjects who take at least 1 dose of any study drug.

5.2.4. Pharmacokinetic Population

Not applicable. The PK analyses will be performed by the Celgene TD group.

5.3. Definitions

5.3.1. Date of First Administration of Study Treatment

The date of first administration of study treatment is derived as the first date that durvalumab, or azacitidine was administered.

For simplicity, the date of first administration of study treatment will also be referred as the start date of study treatment.

5.3.2. Date of Last Administration of Study Treatment

The date of last administration of study treatment is the last date that durvalumab or azacitidine was administered.

5.3.3. Study Day

The study day will be calculated as specified in Section 5.1.2 and will be displayed in the data listings.

5.3.4. Baseline

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 any study drug, unless noted otherwise for a particular assessment. In most cases, baseline assessments are those performed before dosing on Cycle 1, Day 1. However, the last measurement on or prior to the randomization date will be used as the baseline value for subjects who did not take any study drug. Unless otherwise specified in the derived data set specification, the baseline disease characteristics, baseline laboratory value and vital sign that are used in the safety analyses will be derived using this method.

Since the hemoglobin value can be influenced by a red blood cell (RBC) transfusion, the hemoglobin (Hgb) values used in some efficacy analyses are required to satisfy the 7/3-day rule below:

- 7/3-day rule: Only hemoglobin values that are at least 7 days after a transfusion may be used unless there is another transfusion within 3 days after the hemoglobin assessment.

In efficacy analyses, after applying above 7/3-day rule, the baseline hemoglobin value is defined as the last hemoglobin value in 56-days on or prior to randomization.

6. SUBJECT DISPOSITION

Reasons for screen failure will be summarized and listed. Enrollment by country and sites will be summarized by treatment arm within each disease cohort.

A summary of subject disposition (analysis population allocation, subjects randomized, subjects discontinued, along with primary reason for treatment discontinuation and study discontinuation) will be presented for the ITT Population and for the Safety Population and will be summarized using frequencies for both Treatment and Follow-up Periods.

Reasons for discontinuing study treatment will be collected on the CRF and will be summarized for all randomized subjects with the following categories:

- Completed
- Death
- Adverse event
- Progressive disease
- Lack of efficacy
- Withdrawal by subject
- Lost to follow-up
- Protocol violation
- Other

Reasons for discontinuing the study (ie, no follow-up visit and no longer participating in the study) will be collected on the CRF and will be summarized for all randomized subjects with the following categories:

- Completed (per protocol)
- Death
- Adverse event
- Withdrawal by subject
- Lost to follow-up
- Other

Protocol violations / deviations will be summarized and listed by disease cohort and treatment arm for the ITT Population. Protocol violation / deviation will be reported and monitored throughout the study. Data of protocol violation / deviation will be finalized prior to database lock.

The following by-subject listing of subjects with demographic information will be provided:

- Subject listing of discontinuation.

- Subject listing of screen failures.
- Subject listing of protocol violations and protocol deviations.
- Subject listing of being excluded from ITT, EE, Safety or PK Population.

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries using descriptive statistics for the demographics and baseline characteristics will be carried out by disease cohort and treatment arm for each analysis population defined in Section 5.2. Listings will be presented for the ITT Population. Continuous variables will be summarized using descriptive statistics and categorical variables will be summarized with frequency counts and percentages.

7.1. Background and Demographic Characteristics

Age at time of consent (years), weight (kg), height (cm), body mass index (BMI), body surface area (BSA) and other continuous demographic will be summarized using descriptive statistics (eg, mean, standard deviation [STD], median, minimum [Min] and maximum [Max]), while age category (<65 ; ≥ 65 - <75; ≥75), gender, race and other categorical variables will be summarized with frequency counts and percentages.

The below formulas will be used:

BMI (kg/m^2) = weight (kg) / (height * height (m^2)).

BSA (m^2) = (weight (kg)^0.425) * (height (cm)^0.725)*0.007184.

7.2. Baseline Characteristics

Baseline clinical characteristics include temperature (°C), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), pulse (bpm), respiratory rate, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and baseline electrocardiograms (ECGs) will be summarized.

Coagulation test performed at screening will be summarized. Overall interpretation from coagulation test will be summarized along with prothrombin time/international normalized ratio, activated partial thromboplastin time, and thrombin time.

Baseline laboratory assessments from central laboratory will be summarized for Hgb, platelet count, absolute neutrophil count (ANC), white blood cell (WBC) count, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) and total bilirubin.

Creatinine clearance (CrCl) will be assessed at screening by the central laboratory. Creatinine clearance is estimated using the Cockcroft-Gault formula where CrCl(mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976). The CrCl will be summarized as continuous variable. The creatinine clearance will be normalized to an average surface area (size) of $1.73m^2$. The corrected CrCl will be summarized as continuous variable and category variable defined as chronic kidney disease (CKD) stages (Stage 1, 90+; Stage 2, 60-89; Stage 3, 30-59; Stage 4, 15-29; Stage 5, <15).

Cytogenetic risk classifications (Appendix 17.4 and 17.5) will be summarized with frequency counts and percentages. For MDS cohort, IPSS-R will be summarized along with hemoglobin, platelet and absolute neutrophil count used in the derivation. Bone marrow blast will be summarized as continuous variable and category variable as defined in IPSS-R (≤ 2%; > 2% - < 5%; ≥ 5% - ≤ 10%; >10%).

Baseline RBC transfusion burden and platelet transfusion burden will be summarized. The baseline transfusion burden is defined the total number of units of transfusion received before or on the first dose date. Only RBC transfusions given for hemoglobin of ≤ 9.0 g/dL before or on the first dose date will count in the baseline RBC transfusion burden.

The time from initial diagnosis to randomization will also be summarized.

7.3. Medical History

Medical history will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 19.0, or higher. Individual subject listings will be provided. System organ class (SOC) and preferred term (PT) will be summarized by frequency and percentage. Tables will be provided for subjects in the ITT Population and the Safety Population.

7.4. Prior Medications

Prior medications are defined as medications that were started before the start of study treatment (regardless of whether or not they are stopped before the start of the study treatment). Prior medications that are ongoing at the start date of study treatment will also be reported as concomitant medications.

The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization (WHO) (September 2016 version, or higher) will be used to group medications into relevant categories. All prior medications will be summarized by ATC level 1, ATC 3 term term and preferred name in frequency tabulations for the ITT Population and the Safety Population.

7.5. Prior Anticancer Therapy

Whether subject had prior cancer surgery, prior radiation therapy, prior systemic anticancer therapy, prior stem cell transplantation, and prior hormonal anticancer therapy will be summarized with frequency counts and percentages in the ITT population. The number of prior systemic anticancer regimens will be summarized descriptively. In addition, prior exposure to anticancer systemic therapies will also be summarized by ATC level 1 term, ATC 3 term and preferred name with frequency counts and percentages in the ITT Population and the Safety Population.

8. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety Population. Descriptive statistics will be provided for treatment exposure, cumulative dose, average daily dose, treatment compliance, dose intensity, relative dose intensity and dose modifications by disease cohort and treatment arm. Related summary will be provided for each treatment arm across the two disease cohorts. Individual subject listings will be provided to support the tables.

8.1. Treatment Exposure and Duration

Treatment exposure and number of days dosed will be summarized. Total treatment exposure (days) for each study drug is defined as follows:

- Azacitidine: date of first dose through date of last dose + 28 days;
- Durvalumab: date of first dose through date of last dose + 90 days.

Treatment exposure for subjects in the azacitidine alone arm is same as the treatment exposure of azacitidine. Treatment exposure for subjects in the combination arm is defined as date of first dose of any study drug through later one of date of last dose azacitidine + 28 days and date of last dose durvalumab + 90 days. Duration of exposure will be summarized for each arm.

Total number of days dosed is defined as the total number of days with a nonmissing dosing date.

See Section 5.1.3 for cycle definition. Average cycle length (days) and number of treatment cycles will be summarized for each study drug. For azacitidine, average number of days dosed per cycle will be summarized. The number of days dosed per cycle is defined as the number of days with a nonmissing dosing date within that cycle. For average cycle length and average number of days dosed per cycle, a single average value will be computed for each subject and then the descriptive statistics will be provided. Additionally, the count and percent of subjects by number of cycles of treatment will be provided for each treatment.

For each study drug, duration of treatment (days) is defined as:

- (study drug end date) – (date of Cycle 1 Day 1) + 1.

Study drug end date is defined as Min [last non-zero/non-missing dose date + number of days to be covered by the last dose, death date].

The number of days to be covered by the last dose is defined in the table 3.

Table 3: Number of days to be covered by the last dose

IP	Schedule	n = days to be covered by the actual last dose (if schedule respected) *
Durvalumab	CxD1	n=27
Azacitidine	CxD1 to CxD7	n=21

* if schedule is not respected the number of days to be covered by the actual last dose will be adapted accordingly so that the last dose date + n corresponds to the study day 28 of the cycle.

8.2. Cumulative Dose:

The cumulative dose during the treatment is defined as the sum of all doses taken across the treatment period (in mg). Cumulative dose will be calculated separately for azacitidine and durvalumab.

8.3. Average Daily Dose

For each drug, average daily dose (mg/day), defined as the cumulative dose divided by number of days dosed, will be calculated. A single average value will be computed for each subject, overall and within each cycle, and then the descriptive statistics will be computed for each treatment group.

8.4. Treatment Compliance

For each drug, treatment compliance (%) will be calculated for each subject for each cycle of treatment and overall. The compliance is defined as the ratio of the average total daily dose (mg/day) to the average calculated daily dose (mg/day). Calculated daily dose is the prescribed daily dose (mg/m^2) multiplied by the subject's BSA (m^2). Average calculated daily dose is defined as the sum of each calculated daily dose divided by the number of days of scheduled dosing (eg, 7 days / cycle for azacitidine). Compliance for each drug will be summarized using descriptive statistics overall and by cycle.

8.5. Dose Intensity

For each cycle, dose intensity for a study drug is defined as the cumulative dose of the study drug in the cycle divided by the cycle length. The overall dose intensity for each study drug is defined as the cumulative dose divided by the total length of cycles in treatment duration. A single average value will be computed for each subject, overall and within each cycle, and then the descriptive statistics will be computed for each treatment group.

8.6. Relative Dose Intensity

Relative dose intensity is defined as the actual dose intensity divided by the planned dose intensity;

- For durvalumab, the planned dose intensity (mg/day) is 1500 mg / 28 days.

- For azacitidine, the planned dose intensity (mg/day) is 75 mg/m^2* 7 multiplied by the subject's BSA (m^2) / 28 days.

Descriptive statistics of overall and by cycle relative dose intensity will be summarized. Additionally, the number and percentage of subjects will be summarized by category such as ≤ 85% and > 85% for relative total dose intensity of azacitidine, durvalumab, the actual category can be data driven.

8.7. Dose Modification

Dose modifications are permitted in any cycle for appropriate management of AEs or hematological toxicity. Dose reductions are only allowed for azacitidine.

Dose reduction is defined as a nonzero dose administered after the Cycle 1 Day 1 (C1D1) dose which is at a lower dose level than the dose the subject received at the previous dosing day. Dose interruption occurs if the record of actual administered dose is zero except as required by the protocol. If an interruption happens at the start of cycle and causes the cycle to be postponed, it is also called dose delay. Consecutive zeros are counted as one interruption.

Dose reduction or dose interruption will be summarized separately for azacitidine. Summaries include number of subjects who had at least 1 dose reduction (or interruption), time to first dose reduction(or interruption), number of subjects who had at least 1 dose reduction (or interruption) due to AE and time to first dose reduction (or interruption) due to AE will be provided.

Dose interruption as well as infusion interruption will be summarized for durvalumab. Dose delays are summarized for durvalumab only. Number of subjects who had at least 1 interruption, time to the first interruption, number of subjects who had at least 1 interruption due to AE and time to first interruption due to AE will be summarized.

An infusion interruption refers to an interruption of an infusion that actually started.

9. CONCOMITANT MEDICATIONS/PROCEDURES AND SUBSEQUENT THERAPY

9.1. Concomitant Medications

Concomitant mediations are defined as non-study medications that are started during the study treatment exposure period, or started before the start of the study treatment and ended or were ongoing during the study treatment exposure period. The study treatment exposure period is defined as the interval between the date of first administration of any study treatment and the later of 28 days after the last dose of azacitidine and 90 days after the last dose of durvalumab.

All concomitant treatments documented during the study treatment exposure period will be summarized in frequency tabulations by disease cohort for the ITT and Safety Populations. The ATC coding scheme of the WHO (September 2016 version, or higher) will be used to group medications into relevant categories for these tabulations.

Listings of concomitant medications by subject will be provided.

9.2. Concomitant Procedures

The CRF page records procedure, date, and indication. These procedures will be coded using MedDRA Version 19.0 or higher. A frequency summary of subjects by concomitant procedures summarized in frequency tabulations by SOC and preferred term by disease cohort for the ITT Population.

Concomitant procedures will be identified as procedures or surgeries that occurred after or on the date of first dose of durvalumab or azacitidine until 28 days after the last dose of subcutaneous azacitidine and 90 days after the last dose of durvalumab.

9.3. Subsequent Therapy

Whether subject had subsequent radiation therapy, cancer surgery, stem cell transplantation and hormonal anticancer therapy for this disease will be summarized with frequency counts and percentages. In addition, subsequent hormonal anticancer and systemic anticancer therapies will be summarized by ATC level 1 term, ATC 3 term and preferred name for the Safety Population. Details of subsequent therapies will be presented in subjects' data listings.

10. EFFICACY ANALYSIS

All efficacy analyses will be carried out on the ITT Population. Supportive efficacy analyses will also be performed using EE Population.

All efficacy endpoints will be summarized by disease cohort and treatment arm.

All confidence intervals (CIs) will be provided at a level of 95% and between-group comparisons will be provided as appropriate as described below.

10.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR and will be programmatically derived using the results/assessments generated by the central morphologic/cytogenetic and hematology laboratories. In case no central hematology results are available within +/- 8 days of bone marrow samples, local hematology results might be used if available. 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 at least one disease status assessment following treatment Cycle 6. Subjects who discontinue from the treatment phase before the first post baseline efficacy assessment (following treatment Cycle 3) will be replaced unless the subject had a documented progression of their disease or died and will be considered as non-responders. If one post baseline disease assessment is performed, this assessment would be considered for response.

The difference of the proportions for overall response between the azacitidine alone and combination therapy arms will be tested using a standard Wald asymptotic two-sided test with unpooled estimate of variance and presented along with corresponding two-sided 95% CIs.

The hypothesis tested will be:

$H_0: d = 0$

versus

$H_a: d \neq 0,$

Where $d = p_1 - p_2$ is difference in overall response rate in the combination therapy arm (p_1) versus the overall response rate in the monotherapy arm (p2).

The test statistic is

$z = \hat{d}/se(\hat{d})$

Where, the standard error is computed from the sample proportions as

$$se(\hat{d}) = \sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}$$

Where $\hat{p}_1$ (respectively $\hat{p}_2$) is the estimated response rate in the combination therapy arm (respectively monotherapy arm) and is derived as the observed response rates in respective arms.

Myelodysplastic Syndromes Cohort

For the MDS cohort, the primary efficacy endpoint is the proportion of subjects achieving an overall response rate (defined as CR, PR, mCR, and/or HI)) as determined using the International Working Group (IWG) 2006 response criteria for MDS (Appendix 17.2). The ORR will be summarized together with two-sided 95% CI. Subjects discontinued before 6-cycle treatment without achieving overall response will be counted as nonresponders.

The number and percentage of subjects who achieve each component of the overall response (CR, PR, mCR, HI-E, HI-P, HI-N) will be summarized together with associated two-sided 95% CI.

The best overall response per IWG 2006 response criteria will be summarized. The best overall response is defined as the best response prior to progressive disease and first subsequent therapy.

The below order will be considered for the definition of best response:

1. CR
2. PR
3. mCR
4. SD
5. PD
6. Disease transformation
7. Failure due to death
8. Not Evaluable/Missing

Acute Myeloid Leukemia Cohort

For the AML cohort, the primary efficacy endpoint is the proportion of subjects achieving an overall response rate (CR or CRi) based on modified IWG 2003 response criteria for AML (Appendix 17.3). The ORR will be summarized together with two-sided 95% CI. Subjects discontinued before 6-cycle treatment without achieving overall response will be counted as nonresponders.

The number and percentage of subjects who achieve CR, PR, CRi, HI-E, HI-P and HI-N will be summarized together with associated two-sided 95% CI

The best overall response per modified IWG response criteria will be summarized. The best overall response is defined as the best response prior to progressive disease and first subsequent therapy.

The below order will be considered for the definition of best response:

1. CR
2. CRi
3. CRc

4. PR
5. SD
6. PD
7. Treatment failure
8. Not Evaluable/Missing

10.2. Secondary Efficacy Endpoints

Overall response rate and best overall response will also be provided according to the investigator assessment. Of note a response reported as Cytogenetic Complete Remission (CRc) in the eCRF would also be considered as CR in the summaries, CRc being a subset of CR.

Time to event data will be compared between treatment arms within each cohort using a log-rank test stratified according to their cytogenetic risk at time of randomization (intermediate vs poor and very poor for MDS and intermediate vs poor for AML).

Response rates will be compared between treatment groups using the same methodology for the primary endpoint.

Overall Survival

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 earlier between last assessment at which the subject was known to be alive and cut-off date will be used. 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 stratified log rank test will be used to compare the time-to-event curves between Arm A and Arm B. The OS curve and OS at 6 and 12 months will be estimated and compared using Kaplan-Meier (KM) method.

Time-to-Response (TTR)

Time to onset of first response is defined as the time between the date of randomization and the earliest date any response (CR, PR, mCR, or HI for MDS Cohort, CR or CRi for AML Cohort whichever is the 1st) is observed. Subjects who do not achieve any defined response during the treatment period will be censored at the date of last adequate response assessment, disease progression, or death, whichever occurs first. Median time to onset of first response and associated two-sided 95% CI for the treatment group will be estimated using the KM method.

A sensitivity analysis of TTR will be performed for subjects who had responded. Summaries using descriptive statistics n, Mean, Standard Deviation (STD), Q1 and Q3, Median, Minimum (Min), and Maximum (Max) will be provided.

Duration of Response (DoR)

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, PD or death. Duration of response will be censored at the last response assessment date that the subject is known to be progression-free for:

- Subjects who have not relapsed, progressed or died at the time of analysis.
- Subjects who have withdrawn consent or are lost to follow-up prior to documentation of progression.

Censoring rules are defined in Table 4.

Duration of response will be analyzed using the KM method. Median duration of response along with two-sided 95% CI will be provided for each cohort and treatment group.

In addition, the duration of each specific subcategory of response in the MDS Cohort (CR, mCR, PR or HI) and in the AML Cohort (CR) will be summarized using standard descriptive statistics.

Relapse-free Survival (RFS)

Relapse-free survival is defined only for subjects who achieve CR or PR for MDS subjects, CR and CRi for AML subjects, and is measured as the interval from the date of first documented response to the date of disease relapse or death from any cause, whichever occurs first. Subjects who are still alive and relapse-free will be censored at the date of their last response assessment. The RFS curve will be estimated using KM method.

Median RFS along with two-sided 95% CI will be provided for each cohort and treatment group. The RFS at 6 and 12 months will be estimated and compared using Kaplan-Meier (KM) method.

Censoring rules are defined in Table 4.

Cytogenetic Response

External central pathology/cytogenetic reviewers will review the morphologic/cytogenetic data from bone marrow aspirate (BMA), bone marrow biopsies (if performed) 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 (ie subjects with baseline cytogenetic abnormalities), the number and percentage of subjects who achieve the cytogenetic responses will be summarized together with associated two-sided 95% CI.

MDS Cohort:

Progression-free Survival (PFS)

Progression-free survival is calculated as the time from randomization to the first documented progression, relapse 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.

Median PFS along with two-sided 95% CI will be provided for each cohort and treatment group. The PFS at 6 and 12 months will be estimated and compared using Kaplan-Meier (KM) method.

A sensitivity analysis of PFS will be performed, censoring PFS at the time of subsequent systemic anticancer therapy if the subject did not progress before that time.

Transformation to AML and Time to AML Transformation

Number of subjects with 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 (at least 30% of BM blats). Subjects who do not transform to AML will be censored at the date last disease assessment date. Median time to transformation to AML and associated two-sided 95% CI will be estimated using KM method.

AML Cohort:

HI

Rate of HI – erythroid response (HI-E), hematological improvement – platelet response (HI-P) and hematological improvement – neutrophil response (HI-N) according to IWG 2006 response criteria for MDS (Appendix 17.2), will be provided together with Wald asymptotic two-sided 95% CIs.

Table 4: Event and Censoring Rules for Progression-free Survival, Duration of Response, Time-to-Response and Relapse-free Survival

Situation	Date of Progression or Censoring	Situation Outcome
Censoring Rules for PFS and DoR		
Progression	If the first PD is a scheduled assessment then Date of first PD; If the first PD is an unscheduled assessment and no previous assessment, then Date of PD; If the first PD is an unscheduled assessment and has previous assessment, then Date of previous assessment (regardless of the response type).	Event
Death between scheduled assessments or within the first two missed scheduled assessments	Date of death	Event
No progression	Date of last adequate assessment with evidence of no PD	Censored
Death or progression after two or more missed scheduled assessments	Date of last adequate assessment with evidence of no PD; if no adequate assessment exists then censored at date of first dose	Censored
Censoring Rules for RFS		
Relapse	If the first relapse is a scheduled assessment then Date of first relapse; If the first relapse is an unscheduled assessment and no previous assessment, then Date of relapse; If the first relapse is an unscheduled assessment and has previous assessment, then Date of previous assessment (regardless of the response type).	Event
Death between scheduled assessments or within the first two missed scheduled assessments	Date of death	Event
No relapse	Date of last adequate assessment with evidence of no relapse	Censored
Death or progression after two or more missed scheduled assessments	Date of last adequate assessment with evidence of no relapse; if no adequate assessment exists then censored at date of first dose	Censored
Censoring Rules for PFS (sensitivity analysis), DoR and RFS		
Additional therapy received prior to progression or death	Date of additional systemic anticancer therapy	Censored

Censoring Rules for TTR		
Subject responded before PD	First documented response date (CR, PR, mCr, or HI for mDS Cohort, CR or CRi for AML Cohort)	Event
Subject responded after PD	Date of last adequate disease assessment at PD date or death date	Censored
Other case	Date of last adequate disease assessment; if no adequate assessment exists, then censored at date of first dose	Censored

10.3. Eastern Cooperative Oncology Group Performance Status

Shift tables from baseline to best post baseline in ECOG performance score will be displayed by disease cohort and treatment arm for the ITT Population.

CCI [redacted]

[redacted]

[redacted]

11. PHARMACOKINETIC ANALYSIS

Pharmacokinetic concentration data and summary statistics will be tabulated. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods. A separate SAP will provide the details of the statistical methods used to analyze PK data. The results of such an analysis will be reported in a separate report.

12. SAFETY ANALYSIS

This section defines the safety parameters 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.

12.1. Adverse Events

All safety analyses will be conducted using the Safety Population. All analyses will be presented by disease cohort and treatment arm within each disease cohort. Adverse events will be coded according to the MedDRA Version 19.0 or higher. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher.

If a subject experiences multiple AEs under the same PT (SOC), then 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, then 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 (durvalumab or azacitidine) and within 90 days after last dose of durvalumab or 28 days after last dose of azacitidine, as well as those serious TEAEs made known to the investigator at any time thereafter that are suspected of being related to study treatment. 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.

Tables summarizing the incidence of TEAEs by disease cohort and treatment arm will be generated with the following:

- TEAEs;
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab;
- TEAEs of CTCAE grade 3
- TEAEs of CTCAE grade 4
- TEAEs of CTCAE grade 3 or 4;
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab with CTCAE grade 3
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab with CTCAE grade 4
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab with CTCAE grade 3 or 4;
- TEAEs with CTCAE grade 5;

- TEAEs with CTCAE grade 5 related to azacitidine, durvalumab and azacitidine and/or durvalumab;
- Serious TEAEs;
- Serious TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab;
- TEAEs leading to discontinuation of azacitidine, durvalumab and azacitidine and/or durvalumab;
- TEAEs leading to dose reduction of azacitidine;
- TEAEs leading to dose interruption of azacitidine, durvalumab and azacitidine and/or durvalumab;
- TEAEs leading to infusion interruption of durvalumab.

As well as

- TEAEs by cycle of onset;
- Serious TEAEs by cycle of onset;
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab, by cycle of onset;
- TEAEs of CTCAE grade 3 by cycle of onset
- TEAEs of CTCAE grade 4 by cycle of onset;
- TEAEs of CTCAE grade 3 or 4 by cycle of onset;
- TEAEs by maximum CTCAE grade;
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab, by maximum CTCAE grade;
- Common (>=10%) TEAEs;
- Common (>=10%) TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab;
- By age category: <65, 65-74, ≥75
- By gender

Unless otherwise stated, TEAEs will be presented by MedDRA SOC and PT. To facilitate clinical study report writing the following tables will be produced

- TEAEs by PTs
- TEAEs by SOCs
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab by PTs
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab by SOCs
- TEAEs of CTCAE Grade 3 or 4 by PTs, by Grade (3 and 4 separately) and combined (3 or 4 combined)

- TEAEs of CTCAE Grade 3 or 4 by SOCs, by Grade (3 and 4 separately) and combined (3 or 4 combined)
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab of CTCAE Grade 3 or 4 by PTs, by Grade (3 and 4 separately) and combined (3 or 4 combined)
- TEAEs related to azacitidine, durvalumab and azacitidine and/or durvalumab of CTCAE Grade 3 or 4 by SOCs, by Grade (3 and 4 separately) and combined (3 or 4 combined)

All deaths, on treatment deaths, off treatment deaths and causes of death will be summarized. On treatment deaths are defined as deaths occurring within 90 days after the last dose of durvalumab or 28 days after last dose of azacitidine. Off treatment death are defined as deaths occurring after that period. These summaries will be based on the death eCRF page.

Individual subject listing of AEs will be presented. In addition, the following tabulated lists 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

Adverse events of special interests (AESI)

The adverse events of special interest (AESI) refer to a group of PTs from one or more SOCs relating to a defined medical condition or area of interest. Unless an AESI is defined by a single PT the AESI generally refers to a group of PTs, rather than the individual PTs.

AESIs will be summarized separately for azacitidine and durvalumab, The AESI summary for each study treatment will be summarized by AESIs, which will be referred as AESI categories in tables and listings, and by PT.

The following AESIs for azacitidine based on risk definitions (search criteria) as outlined in the Vidaza risk management plan (RMP) currently approved at the time of data cut-off will be summarized:

- Myelosuppression (Neutropenia, thrombocytopenia, anemia, general myelosuppression)
- 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
- Gastrointestinal disorders as defined by MedDRA SOC

Below are the AESIs for durvalumab for regulatory purposes:

- Adrenal insufficiency
- Colitis
- Dermatitis
- Diarrhoea
- Diabetes Mellitus Type 1
- Hyperthyroidism
- Hypophysitis
- Hypothyroidism
- Infusion related/Hypersensitivity/Anaphylactic reactions
- Select renal events
- Select pancreatic events
- Pneumonitis
- Rash
- Select hepatic events
- Other rare/miscellaneous

After review of the data, there may be other AESIs identified. The following summaries will be provided for TEAEs included in the above-mentioned AEs of special interest:

- All TEAEs
- All TEAEs by cycle of onset
- TEAEs of Grade 3
- TEAEs of Grade 4
- 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.

12.2. Clinical Laboratory Evaluations

Descriptive statistics of observed and change from baseline values will be presented.

Clinical laboratory values will be graded according to CTCAE Version 4.03 or higher for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shifts from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided.

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. Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests.

Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data.

CCI [redacted]

12.4. Vital Sign Measurements

For vital signs with shifts from baseline to worst during treatment (below, within, and above the normal ranges) will be displayed in cross–tabulations. Summary statistics (N, Mean, STD, median, Q1, Q3 Min, and Max) of observed and change from baseline values will be presented.

Normal ranges are defined as follows:

- Systolic blood pressure (SBP) → Normal (100 – 140 mm Hg, inclusive)
- Diastolic blood pressure (DBP) → Normal (60 – 90 mm Hg, inclusive)
- Body temperature → Normal (35 – 38°C, inclusive)
- Pulse → Normal (60 – 100 bpm, inclusive)
- Respiration → Normal (12 – 20 BPM, inclusive).

12.5. Electrocardiogram

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with "Normal", "Abnormal, not clinically significant, and "Abnormal, clinically significant". Baseline and end of treatment (EOT) in the overall ECG interpretation will be displayed in cross-tabulations.

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[redacted]

14. INTERIM ANALYSIS

14.1. General Information

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

An interim analysis for futility purposes following the completion of first stage will be conducted. The primary analysis will be conducted following the completion of second stage. The decision to proceed to Stage 2 after completion of Stage 1 will be performed independently in each cohort as mentioned below.

The DMC will review the safety data on a regular basis.

Myelodysplastic Cohort

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 (CR. mCR, PR or HI) or discontinued due to death or disease progression. Subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the interim analysis.

The MDS cohort will be completed to include a total of 72 MDS subjects. Details of futility rules are given in section 4.3.1.

Acute Myeloid Leukemia Cohort

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 (CR or CRi) or discontinued due to death or disease progression. Subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from the interim analysis.

The AML cohort will be completed to include a total of 110 AML subjects. Details of futility rules are given in section 4.3.2.

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

14.2. Statistical Approaches for Control of Alpha

The interim analysis is for futility purposes, type I error will be well controlled.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

Response derivations have been updated for consistency with IWG Response Criteria in Myelodysplasia (Cheson, 2006) and Modified IWG AML Response Criteria (Cheson, 2003).

IA requirements and definition of EE population have been detailed in order to specify that subjects assigned to Arm A, who received less than 3 cycles of durvalumab and continued under azacitidine monotherapy are to be excluded from interim analysis and/or in the EE population.

16. REFERENCES

CCI [redacted]

Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet.*Blood*. 2010;115:453-474.

Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3).

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA/CDER/CBER May 2007.

CCI [redacted]

Sekeres MA and Cutler C. How we treat higher-risk myelodysplastic syndromes. *Blood*. 2014;123:829-836.

17. APPENDICES

17.1. Date Imputation Guideline

17.1.1. Impute Missing AE/Prior or Concomitant Medications Start Dates

If the stop date is nonmissing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is **same** as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields
- If the year is **prior to** the year of first day on study medication, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- Included as TEAE

17.1.2. Impute Missing AE/ Prior or Concomitant Medications Stop Dates

If the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dose date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

17.1.3. Impute Missing Disease Diagnosis Dates

For partial diagnosis dates, January will be assigned to the missing month; and the first day of the month will be assigned to the missing day.

17.1.4. Impute Missing Dates in Prior Cancer Regimen

For each prior cancer regimen, the regimen start/stop date, disease progression date, best response date, and date of first response for PR or better, will be collected. If the day of any date is missing, then the first day the nonmissing month will be assigned to the missing day; if month or year of the date is missing, the date will not be imputed and treated as missing.

17.1.5. Impute Missing Dates in Subsequent Cancer Therapy

Subject will allow take other antimyeloma therapy after discontinued from the study. The cancer therapy start/stop date will be collected. If the day of any date is missing, then the last day the nonmissing month will be assigned to the missing day; if day and month are both missing, then the December 31 of the nonmissing year will be assigned to the missing day.

17.2. International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006)

Altering Disease Natural History	
Complete remission (CR)	▪ BM Blasts ≤ 5% **AND** ▪ All of the following peripheral blood values met: ▪ Hemoglobin ≥ 11 g/dL ▪ Platelets ≥ 100 x109/L ▪ ANC ≥ 1.0 x109/L ▪ Peripheral Blasts=0% Labs must meet criterion for at least 28 consecutive days. If not confirmed for 28 days then response should be mCR. In addition ▪ The 7/3 rule should be applied to Hemoglobin. ▪ Platelets collected 3 days period following Platelet transfusion will not be used - ANC values that must be at least 14 days following a G-CSF application
Partial remission (PR)	▪ BM Blasts decreased by ≥ 50% over pretreatment but still > 5% **AND** ▪ All of the following peripheral blood values met: ▪ Hemoglobin ≥ 11 g/dL ▪ Platelets ≥ 100 x109/L ▪ ANC ≥ 1.0 x109/L ▪ Peripheral Blasts=0% Labs Must meet criterion for at least 28 consecutive days. In addition ▪ The 7/3 rule should be applied to Hemoglobin. ▪ Platelets collected 3 days period following Platelet transfusion will not be used ANC values that must be at least 14 days following a G-CSF application

Marrow CR	▪ Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment with baseline BM blast >5% **AND** ▪ Not all of the following peripheral blood values met or none are met: ▪ Hemoglobin ≥ 11 g/dL ▪ Platelets ≥ 100 x109/L ▪ ANC ≥ 1.0 x109/L ▪ Peripheral Blasts=0% Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Any evaluable time point where criteria for all other response categories (i.e., CR, PR, PD, Failure due to death, Not Assessable) are not met
Failure	Death during treatment
Disease Progression (PD)	▪ If condition for Transformation to AML and relapse after CR/PR are not verified ▪ For patients with: ▪ Nadir value less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts ▪ Nadir value 5% - 10% blasts: ≥ 50% increase in blasts to > 10% blasts ▪ Nadir value 10% - 20% blasts: ≥ 50% increase in blasts to > 20% blasts AND ANY OF THE FOLLOWING ▪ ≥ 50% decrement from max level of ANC and ANC < 1.0 GI/L OR ▪ ≥ 50% decrement from max level of Platelets and Platelets < 100 GI/L OR ▪ Reduction from max level of Hgb ≥ 20 g/L and Hgb < 110 g/L OR • Transfusion dependence (apply to baseline TI subjects only)

[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.

Altering Disease Natural History	
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	• BM % blast >= baseline % blast and BM % blast >= 5% **OR** • ≥ 50% decrement from max level of ANC and ANC < 1.0 GI/L **OR** • ≥ 50% decrement from max level of Platelets and Platelets < 100 GI/L **OR** • Reduction from max level of Hgb ≥ 20 g/L and Hgb < 110 g/L **OR** • RBC/platelet transfusion is given after CR/PR

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 in >=8 weeks **OR** ▪ 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 ▪ For Hgb, 7/3 rule should be applied first
Platelet response (HI-P) (Pretreatment < 100×10^9/L)	▪ in >=8 weeks Absolute increase of ≥ 30 × 109/L for patients starting with > 20 × 109/L **OR** ▪ Increase from <= 20 × 109/L to > 20 × 109/L and by at least 100%

Neutrophil response (HI-N) (Pretreatment < 1.0×10^9/L)	▪ in >=8 weeks At least 100% increase and an absolute increase from mean of pre-dose of > 0.5 × 109/L

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.

17.3. Modified International Working Group AML Response Criteria (Cheson, 2003)

Hematologic Response According to IWG Criteria for AML

Category	Definition
Morphologic Complete Remission (CR)	• BM Blasts < 5% **AND** • All of the following peripheral blood values met: ○ Platelets ≥ 100 x109/L ○ ANC ≥ 1.0 x109/L Where the date of the hematology assessment used is within the window -8 and +8 days of BM date. If multiple hematology assessments within this window, the closest to BM date should be used. If multiple on same distance to BM date, the one before BM date should be used **AND** • No platelet, or whole blood transfusions for 1 week (7days) prior to the date of the hematology assessment used for the response evaluation
Morphologic Complete Remission with Incomplete Blood Count Recovery (CRi)	▪ BM Blasts < 5% AND ▪ One or both of the following peripheral blood values met: ▪ Platelets < 100 x109/L ▪ ANC < 1.0 x109/L Where the date of the hematology assessment used is within the window -8 and +8 days of BM date. If multiple hematology assessments within this window, the closest to BM date should be used. If multiple on same distance to BM date, the one before BM date should be used

Category	Definition
Cytogenetic Complete Remission (CRc)	▪ CR criteria met **AND** ▪ Abnormal karyotype present at baseline **AND** Reversion to normal karyotype at time of CR (based on ≥ 10 metaphases), where date of cytogenetic sample = date of BM sample used for the CR assessment
Partial Remission (PR)	▪ One of the following BM Blasts values met: ▪ BM blasts of 5% to 25% (inclusive) when baseline BM blasts is 50% to 100% (inclusive) ▪ BM blasts ≥ 5% and 50% decrease from baseline when baseline BM blasts is <= 49% (inclusive) **AND** ▪ All of the following peripheral blood values met: ▪ Platelets ≥ 100 x109/L ▪ ANC ≥ 1.0 x109/L Where the date of the hematology assessment used is within the window -8 and +8 days of BM date. If multiple hematology assessments within this window, the closest to BM date should be used. If multiple on same distance to BM date, the one before BM date should be used
Relapse after CR or CRi	▪ > 5% blast in peripheral blood following CR or CRi **OR** > 15% BM blast following CR or CRi
Treatment Failure	▪ Death w/death date during Cycle 1 **OR** • Death w/death date ≤ 28 days after last dose date and prior to C2D1

Category	Definition
Progressive Disease[b]	▪ If the lowest/best response %BM blast is <= 70%, PD is defined when there's an increase of %BM blast of at least 50%. If the lowest/best response %BM blast is > 70% instead, PD is defined when there's an increase of %BM blast of at least 10% (absolute increase). If %BM blast doesn't increase more than 10%, PD is defined as an increase of at least 2x in %PB blast from the lowest/best response with %PB blast > 10%.
Stable disease	▪ Any evaluable time point where criteria for all other response categories (i.e., CR, CRi, PR, PD, Treatment failure, Not Assessable) are not met

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

17.4. 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 ($\times 10^9$/L)	≥100	50 - < 100	< 50	-	-	-	-
ANC ($\times 10^9$/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 syndrome. Blood. 2012;120(12):2454-65

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

17.5. 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.

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