# B9991011 – PHASE 1B

# PHASE 1B/PHASE 3 MULTICENTER STUDY OF AVELUMAB (MSB0010718C) IN COMBINATION REGIMENS THAT INCLUDE AN IMMUNE AGONIST, EPIGENETIC MODULATOR, CD20 ANTAGONIST AND/OR CONVENTIONAL CHEMOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

## JAVELIN DLBCL

## STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Compounds:** | MSB0010718C<br>PF-05082566 |
| **Compound Name:** | Avelumab<br>Utomilumab |
| **Version:** | 2.0 |
| **Date:** | 12-Feb-2018 |

## TABLE OF CONTENTS

## LIST OF TABLES



## APPENDICES

## 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991011 is based on the protocol amendment 3 dated 11DEC2017.

CCI

CCI

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991011 – Phase 1b. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, pharmacokinetic (PK) concentrations and parameters, immunogenicity parameters, minimal residual disease (MRD), biomarkers). The primary analysis will include all data up to a cut-off date corresponding to 12 months (52 weeks) after the last patient is randomized. The final analysis of the data will be performed after last patient last visit (LPLV) in the study.

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

### 2.1. Study Objectives

**Primary Objectives**

- To assess safety, efficacy, and potentially select the most active treatment regimen among 3 treatment arms to advance to the Phase 3 component of the study.

**Secondary Objectives**

- To evaluate the PK of each treatment arm;
- To assess the immunogenicity of each treatment arm;

- To evaluate PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarkers with their relationship to selected clinical response parameters;

- To evaluate the relationship between minimal residual disease burden as assessed using serial blood samples with selected clinical response parameters.

CCI [redacted]

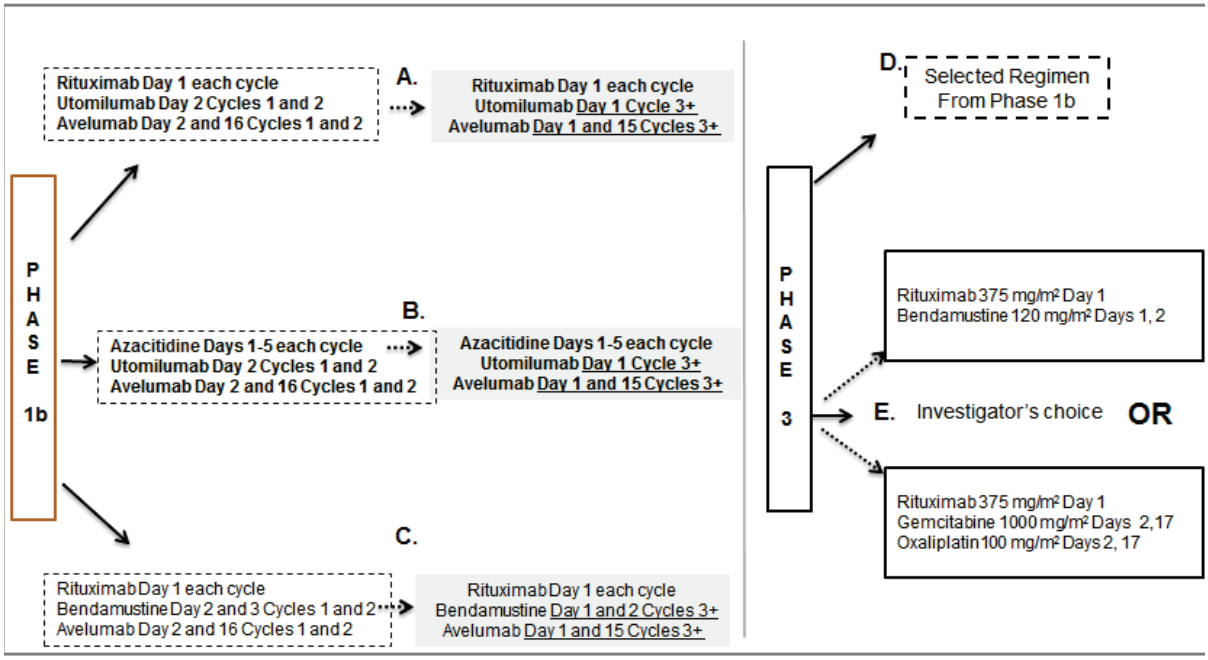
## 2.2. Study Design

Study B9991011 is a multicenter, international, parallel-arm, randomized, open-label, 2-component (Phase 1b followed by Phase 3) study of avelumab in combination with:

(i) rituximab (CD20 antagonist) and utomilumab (4-1BB agonist);

(ii) azacitidine (DNA methyltransferase inhibitor [DNMTi]) and utomilumab (4-1BB agonist), and

(iii) rituximab (CD20 antagonist) and bendamustine (chemotherapy).



The target study population of this Phase 1b/Phase 3 registrational study will comprise patients with relapsed/refractory (R/R) DLBCL following at least 2 (but not more than 4) lines of prior rituximab/multi-agent chemotherapy, and/or failed ASCT, or who are not eligible for intensive chemotherapy or candidates for ASCT.

The primary objective of Phase 1b is to make a preliminary assessment of dose-limiting toxicities in each treatment arm (N=6 each), and then potentially select a treatment regimen to be advanced to Phase 3 based on efficacy including the observed ORR (as assessed by the Investigator) and safety profile in each expanded treatment arm (N =28 each).

It is expected that up to 84 patients will be randomized among three treatment arms (28 patients each) in Phase 1b.

In order to determine which treatment arm should be evaluated in Phase 3, pre-specified Go/No Go criteria are configured to identify with ≥95% confidence a treatment regimen that is superior to rituximab /bendamustine benchmark data (ie, historical reference control) with respect to one or more of the following (in a hierarchical manner):

1. Objective Response Rate (ORR) (ie, proportion of patients achieving CR or PR).
2. 6-month Durable Response Rate (DRR) (ie, proportion of patients with CR or PR persisting for at least 6 months).
3. Progression-free survival (PFS) rate at 6 months.

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

### 3.1. Primary Endpoints

- Dose Limiting Toxicity (DLT):

  Severity of adverse events (AEs) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For the purpose of selecting the regimen to advance into Phase 3, any of the AEs listed below occurring during the DLT observation period (4 weeks from the time of the first study treatment administration (Cycle 1, Day 1) until the planned administration of the second cycle that are attributable to an agent in the combination (and not incontrovertibly related to underlying disease or intercurrent illness), will be classified as DLTs.

  Hematologic:

  - Grade 4 neutropenia (absolute neutrophil count [ANC] <500 cells/mm3) not recovering to ≤ Grade 3 lasting >7 days (despite the use of G-CSF).
  - Grade ≥ 3 febrile neutropenia (ANC <1000/mm3) with a single temperature of >38.3 degrees Celsius (>101.0 degrees Fahrenheit) or a sustained temperature of ≥38.0 degrees Celsius (100.4 degrees Fahrenheit) for more than 1 hour, with or without associated sepsis or that leads to a delay in the next cycle of therapy (despite the use of G-CSF).

- Grade ≥3 neutropenic infection (despite the use of G-CSF).
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with clinically significant bleeding (requiring red cell transfusion).
- Grade 4 anemia (despite red blood cell transfusion).

Non-Hematologic:

Any Grade ≥3 toxicity, except for the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever controlled with standard medical management.
- Transient (≤24 hours) Grade 3 fatigue, localized skin reactions, or headache that resolves to Grade ≤1.
- Grade 3 nausea, or vomiting resolved to Grade <1 in <72 hours following the initiation of adequate medical management.
- Grade 3 diarrhea that resolved to Grade ≤1 in <72 hours following the initiation of adequate medical management.
- Grade 3 skin toxicity resolved to Grade ≤1 in <7 days.
- Tumor flare.
- Single laboratory values that are out of the normal range, that do not have any clinical correlate, and resolve to Grade <1 within 7 days with adequate medical management.

Abnormal laboratory tests should be repeated. While the rules for adjudicating DLTs in the context of selecting the regimen to advance to Phase 3 clinical trial are specified above, AEs not listed above, or any AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT following consultation between the Sponsor and the Investigator, based upon the overall emerging safety profile.

- Objective Response (OR) as assessed by the Investigator per Lugano Response Classification Criteria.

OR is defined as complete response (CR) or partial response (PR) according to Response Criteria for Malignant Lymphoma from the date of randomization until the date of the first documentation of progressive disease (PD).

## 3.2. Secondary Endpoints

### 3.2.1. Safety Endpoints

- AEs as graded by NCICTCAE v4.03;

  AEs will be graded by the investigator according to CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

- Laboratory abnormalities as graded by NCI CTCAE v4.03;

- Vital signs (blood pressure, heart rate);

- Electrocardiogram (ECG).

### 3.2.2. Efficacy Endpoints

- Duration of Response (DR), Time to Tumor Response (TTR), Disease Control (DC), Progression-free survival (PFS), as assessed by the Investigator per Lugano Response Classification Criteria and Overall Survival (OS).

  DR is defined, for patients with an objective response (OR), as the time from the first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause.

  DC is defined as CR, PR, or SD. Criterion for SD must have been met at least 6 weeks after the date of randomization.

  TTR is defined, for patients with an OR, as the time from the date of randomization to the first documentation of objective response (CR or PR).

  PFS is defined as the time from the date of randomization to the date of the first documentation of PD or death due to any cause, whichever occurs first.

  OS is defined as the time from the date of randomization to the date of death due to any cause.

### 3.2.3. Pharmacokinetic Endpoints

- Pharmacokinetics: PK parameters of avelumab, rituximab, utomilumab, azacitidine and bendamustine, as data permit: maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration time curve from time 0 to $\tau$ hours post dose ($AUC_{0-\tau}$, where $\tau$ is dependent on the analyte) apparent plasma clearance (CL/F), and apparent volume of distribution (V/F) each analyte following single and multiple dosing.

**Table 2. PK Parameters to be Determined for Avelumab, Rituximab, Utomilumab, Azacitidine, Bendamustine and its M3 Metabolite**

| Parameter[a] | Definition | Method of Determination |
|---|---|---|
| $AUC_{last}$ | Area under the serum/plasma concentration-time profile from time zero to the time of the last quantifiable concentration ($C_{last}$) | Linear/Log trapezoidal method |
| $AUC_{sd,\tau}$<br><br>$AUC_{ss,\tau}$ | Area under the serum/plasma concentration-time profile from time zero to the next dose (after single dose and at steady state) | Linear/Log trapezoidal method |
| $AUC_{sd, inf}$ | Area under the serum/plasma concentration-time profile from time zero to infinity | $AUC_{sd, inf} = AUC_{last} + (C_{last}/K_{el})$ |
| $C_{max}$<br><br>$C_{ss, max}$ | Maximum observed serum/plasma concentration (after single dose and at steady state) | Observed directly from data |
| $T_{max}$<br><br>$T_{ss, max}$ | Time of $C_{max,sd}$<br><br>Time of $C_{max, ss}$ | Observed directly from data as time of first occurrence |
| $t_{½}$ | Terminal half-life | $Log_e(2)/k_{el}$,<br><br>where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression. |
| $C_{trough}$ | Predose concentration during multiple dosing | Observed directly from data |
| $C_{ss, av}$ | Average concentration during multiple dosing | $AUC_{ss,\tau} / \tau$ |
| CL or CL/F | (Apparent) clearance | Dose /$AUC_{sd, inf}$ after single dose<br><br>Dose / $AUC_{ss, \tau}$ at steady state |
| $V_z$ or $V_z$/F | Apparent volume of distribution | Dose / ($AUC_{sd, inf} \cdot k_{el}$) after single dose<br><br>Dose / ($AUC_{ss, \tau} \cdot k_{el}$) at steady state |
| $R_{ac}$ | Accumulation ratio | $AUC_{ss, \tau}$ / $AUC_{sd, \tau}$ |
| $T_{last}$ | The last time point of the last quantifiable concentration ($C_{last}$) | Observed directly from data |

[a] If data permit

### 3.2.4. Immunogenicity Endpoints

- Anti-Drug Antibody (ADA); neutralizing antibodies (nAb) against avelumab, utomilumab and rituximab.

### 3.2.5. Biomarker Endpoints

- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline;

- MRD burden as assessed using serial blood samples.

CCI [redacted]

[redacted]

[redacted]

### 3.4. Baseline Variables

#### 3.4.1. Study Drug, Study Treatment and Baseline Definitions

In Phase 1b, '**study drug**' refers to avelumab, utomilumab, azacitidine, rituximab or bendamustine, and '**study treatment**' (or '**treatment arm**') refers to one of the following:

- Arm A: avelumab/rituximab/utomilumab;
- Arm B: avelumab/azacitidine/utomilumab;
- Arm C: avelumab/bendamustine/rituximab.

**Start and end dates of study treatment**

- The date/time of first dose of study treatment in a combination arm is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.
- The date/time of last dose of study treatment in a combination arm is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

**Definition of baseline:**

Definition of baseline for efficacy CCI [redacted] analyses

The last measurement prior to randomization will serve as the baseline measurement for efficacy CCI [redacted] analyses. If such a value is missing, the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessments data where the baseline assessment would be considered as missing.

Definition of baseline for immunogenicity analyses:

The last available assessment prior to the start of treatment with the given biologic (ie, rituximab, utomilumab, avelumab) is defined as 'baseline' result or 'baseline' assessment. If per protocol an assessment is planned to be performed prior to the first dose of the given biologic and the assessment is performed on the same day as the first dose of that biologic but the assessment time point is not collected or is missing, it will be assumed that the assessment was performed prior to the biologic's administration.

Definition of baseline for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

### 3.4.2. Baseline Characteristics

Baseline characteristics (including demographics, physical measurements, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

## 3.5. Safety Endpoints

### 3.5.1. Adverse Events

**Treatment-Emergent Adverse Events**

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period.

**On-treatment period** is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

**Adverse Events of Special Interest (AESIs)**

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendices 1 and 2, respectively.

## 4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

### 4.1. Full Analysis Set

The full analysis set (FAS) will include all randomized patients. Patients will be classified according to the study treatment assigned at randomization.

### 4.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case patients will be classified according to the first study treatment received.

### 4.3. Other Analysis Sets

#### 4.3.1. DLT-evaluable Analysis Set

The DLT-evaluable Analysis Set is a subset of the safety analysis set and includes randomized patients in each arm who are eligible for the study, receive at least 1 dose of study treatment, and either experience DLT during the first cycle, or complete the primary DLT observation period of 4 weeks.

Patients without DLTs who withdraw from study before completing the 4-week DLT observation period for reasons other than toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

#### 4.3.2. PK Analysis Sets

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab, utomilumab, rituximab, bendamustine or its M3 metabolite, or azacitidine.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for avelumab, utomilumab, rituximab, bendamustine or its M3 metabolite, or azacitidine.

### 4.3.3. Biomarker Analysis Set

The Biomarker Analysis Set is a subset of the safety analysis set and will include all patients who have at least one baseline biomarker assessment. Analysis sets will be defined separately for blood-based, fecal stool-based, and tumor tissue-based biomarkers.

### 4.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one ADA/nAb sample collected for avelumab, utomilumab or rituximab.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

### 5.1.1. Hypotheses and Sample Size Determination

Approximately 84 patients will be randomized 1:1:1 among three treatment arms (28 patients/arm) in Phase 1b.

There is no formal hypothesis testing for safety. However before expanding randomization past the first 6 and/or 12 DLT-evaluable patients in each treatment arm, safety must be confirmed in the first 6 and/or 12 patients evaluable for DLT in each treatment arm.

For efficacy, within each treatment arm, the following hypothesis will be tested

$$H_0: \text{ORR} \leq 46\%, \text{ versus } H_1: \text{ORR} > 46\%$$

at 1-sided significance level of 0.025. With 28 patients per treatment arm, there is 79.7% power to reject $H_0$ if the true ORR under $H_1$ is ≥73%.

### 5.1.2. Decision Rules

A Pfizer Internal Review Committee (IRC) evaluation of the first 6 and/or 12 DLT-evaluable patients in each treatment arm will occur after the last patient has completed one cycle of treatment. Enrollment will be halted while the first 6 DLT-evaluable patients in each treatment arm are evaluated for safety.

Up to 12 DLT-evaluable patients will be randomized into each treatment arm in the Phase 1b and evaluated for DLT during the first cycle of treatment as follows:

- Randomize and treat up to 6 DLT-evaluable patients in each treatment arm:
    - If ≤1 of 6 patients experience DLT, the treatment arm will be expanded to randomize up to 28 patients;
    - If ≥3 of up to 6 patients experience DLT, randomization in the specific treatment arm will be discontinued;
    - If 2 of 6 patients experience DLT, the treatment arm will be expanded to randomize to 6 additional DLT-evaluable patients;

- If ≤3 of 12 patients experience DLT, the treatment arm will be expanded to randomize up to 28 patients;

- If ≥4 of up to 12 patients experience DLT, randomization in the specific treatment arm will be discontinued.

The efficacy of each treatment combination will be evaluated using pre-specified Go/No-Go criteria configured to identify with ≥95% confidence a treatment regimen that is superior to rituximab/bendamustine benchmark data (historical reference control) with respect to one or more of the following in a hierarchical manner: ORR, 6-month DRR and PFS rate at 6 months. In the final analysis of the phase 1b the decision-making process will include the following steps:

1. In each treatment arm, $H_0$: ORR ≤46 vs $H_1$: ORR >46%) will be tested at 1-sided $\alpha$=0.025 using the binomial distribution;

2. If $H_0$ for ORR is not rejected for any of the three treatment arms, the study will not proceed to Phase 3;

3. If only one treatment arm meets the ORR criterion, then that treatment arm will be evaluated in Phase 3;

4. If ≥2 treatment arms meet the ORR criterion, then the selection of the treatment arm will be based on the 6-month DRR criterion. In each treatment arm, $H_0$: 6-month DRR ≤23% vs $H_1$: 6-month DRR >23% will be tested at 1-sided $\alpha$=0.025 using the binomial distribution;

5. If only one treatment arm meets the 6-month DRR criterion, then that treatment arm will be evaluated in Phase 3;

6. If none or >1 treatment arm meets the 6-month DRR criterion, then the selection of the treatment arm will be based on the PFS rate at 6 months. In each treatment arm, $H_0$: PFS rate at 6 months ≤31% vs $H_1$: PFS rate at 6 months >31% will be tested at a 1-sided $\alpha$=0.025 using the binomial distribution;

7. If only one treatment arm meets the PFS rate at 6 months criterion, then that treatment arm will be evaluated in Phase 3;

8. If none, or >1 treatment arm meets the PFS rate at 6 months criterion, then the totality of safety and efficacy data will be taken into consideration when determining which arm to take forward into the Phase 3.

In addition, there will be a formal interim analysis (IA), performed 13 weeks after 8 patients in each treatment arm have been randomized. The purpose of the IA in the Phase 1b component of the study is to allow for early stopping of any treatment arm for futility based on ORR. The cutoff for the IA is 13 weeks after 8 patients in each treatment arm have been randomized. If ≤2 responses are observed for 8 patients in a treatment arm, further enrollment in the treatment arm may be stopped.

Table 3 provides the conditional power of the Phase 1b when the futility boundary is crossed at the time of the IA based on the test of hypothesis described in Section 5.1.1.

**Table 3. Conditional Power for the Phase 1b Based on the Interim Analysis Results**

| Responders/Number of patients | True ORR=50% | True ORR=60% | True ORR=73% |
|---|---|---|---|
| 0/8 | <0.001 | 0.001 | 0.016 |
| 1/8 | <0.001 | 0.004 | 0.064 |
| 2/8 | 0.001 | 0.016 | 0.170 |

## 5.2. General Methods

As described in Section 3.4.1, in Phase 1b '**treatment arm**' refers to one of the following:

- Arm A: avelumab/rituximab/utomilumab;
- Arm B: avelumab/azacitidine/utomilumab;
- Arm C: avelumab/bendamustine/rituximab.

Baseline characteristics, disposition and efficacy data will be summarized based on the FAS by treatment arm.

DLTs will be summarized based on the DLT-evaluable Analysis Set by treatment arm.

Other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the Safety Analysis Set by treatment arm.

PK data will be summarized based on the PK Analysis Set by treatment arm.

Biomarker data will be summarized based on the Biomarker Analysis Set by treatment arm.

Immunogenicity data will be summarized based on the Immunogenicity Analysis Set by treatment arm.

PRO data will be summarized based on the FAS Analysis Set by treatment arm.

### 5.2.1. Data Handling After the Cut-off Date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

### 5.2.2. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients randomized/treated at each center.

### 5.2.3. Presentation of Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

### 5.2.4. Definition of Study Day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

### 5.2.5. Definition of Start of New Anti-cancer Drug Therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

### 5.2.6. Definition of Start of New Anti-cancer Therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the date of randomization amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages.
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'.
- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

### 5.2.7. Definition of On-treatment Period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

### 5.2.8. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25.
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth).
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth).

The integer part of the calculated age will be used for reporting purposes.

- BMI ($kg/m^2$) = weight (kg)/[height (m)]$^2$.

- BSA ($m^2$) = ([height (cm) × weight (kg)] / 3600)$^{0.5}$.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

#### 5.2.9. Unscheduled Visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

#### 5.2.10. Adequate Baseline Tumor Assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 42 days prior to and including the date of randomization.

- All documented lesions must have non-missing PET scores.

#### 5.2.11. Adequate Post-baseline Tumor Assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, or PD can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

### 5.3. Methods to Manage Missing Data

#### 5.3.1. Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg, when they cannot be calculated, should be presented as ‘ND’ or ‘NA’. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as ‘ND’ or ‘NA’.

#### 5.3.1.1. Pharmacokinetic Concentrations

**Concentrations Below the Limit of Quantification**

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

**Deviations, Missing Concentrations and Anomalous Values**

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

#### 5.3.1.2. Pharmacokinetic Parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

### 5.3.2. Handling of incomplete Dates

#### 5.3.2.1. Disease History

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15$^{th}$ day of the month.

- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.

- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.

- If the date is completely missing, no imputation will be performed.

#### 5.3.2.2. Adverse Events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.

- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.

- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.

- In all other cases the missing onset day or missing onset month will be replaced by 1.

- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

#### 5.3.2.3. Prior and Concomitant Medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.

- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.

- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.

- In all other cases the missing medication day or missing medication month will be replaced by 1.

- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete medication stop date will not be imputed.

#### 5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date.

- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date).

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date).

  = min (EOT date, death date), for all other cases.

### 5.3.3. Imputation Rules for Date of Last Contact and Efficacy Assessments

#### 5.3.3.1. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments).

- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.

- AE start and end dates.

- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive').

- Study drug start and end dates.

- Randomization date.

- Withdrawal of consent date.

- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

#### 5.3.3.2. Death Date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact.

- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

#### 5.3.3.3. Tumor Assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the

following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

#### 5.3.3.4. Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below.
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy.
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is derived as follows:
  - <u>Start date of new anti-cancer therapy is completely missing.</u>

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy].
  - <u>Only year (YYYY) for start of anti-cancer therapy is available.</u>

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

    THEN imputed start date = 01JANYYYY.
  - <u>Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available.</u>

IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY ;

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy].

THEN

imputed start date = 01 MMM YYYY.

# 6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology. All analysis described in what follows apply to patients enrolled in Phase 1b.

## 6.1. Primary Endpoints

### 6.1.1. DLTs

#### 6.1.1.1. Primary Analysis

DLTs will be graded according to NCI-CTCAE version 4.03 and coded using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

For the first 6 and/or 12 DLT-evaluable patients in each treatment arm, the number and percentage of patients with DLTs will be listed and summarized by treatment arm, primary SOC and PT in decreasing frequency based on the frequencies observed for treatment arm A.

### 6.1.2. Objective Response as Assessed by the Investigator per Response Criteria for Malignant Lymphoma

#### 6.1.2.1. Primary Analysis

The following analyses will be based on the FAS by treatment arm. Assessment of response will be made using Response Criteria for Malignant Lymphoma. Assessments below refer to investigator assessment.

**Best overall response (BOR)** will be assessed based on reported overall lesion responses at different evaluation time points from the date of randomization until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

- CR = CR documented before first documentation of PD.
- PR = PR documented before first documentation of PD (and not qualifying for a CR).
- SD = at least one SD assessment (or better) ≥6 weeks after the date of randomization and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD after the date of randomization (and not qualifying for CR, PR, SD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR.

**Objective Response (OR)** is defined as BOR of CR or PR according to Response Criteria for Malignant Lymphoma.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment arm will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of patients with a BOR of CR, PR, SD, PD, and NE will be tabulated. Patients with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment.
- No post-baseline assessments due to death.
- No post-baseline assessments due to other reasons.
- All post-baseline assessments have overall response NE.
- New anti-cancer therapy started before first post-baseline assessment.
- SD of insufficient duration (<6 weeks after the date of randomization).

## 6.2. Secondary Endpoint(s)

### 6.2.1. Safety Endpoints

Refer to Section 6.6.

### 6.2.2. Efficacy Endpoints

The following analyses will be based on the FAS by treatment arm. Assessment of response will be made using Response Criteria for Malignant Lymphoma. Tumor-related endpoints will be analyzed based on investigator assessment.

#### 6.2.2.1. Tumor Shrinkage from Baseline

Tumor shrinkage will be summarized as the percent change from baseline in lymph nodes and extranodal sites (sum of the product of the diameters (SPD)) per time point. It will be derived as:

- ((SPD at week XX – SPD at baseline)/SPD at baseline) × 100.

The maximum reduction in lymph nodes and extranodal sites from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((SPD at week XX – SPD at baseline)/SPD at baseline) × 100.

A waterfall plot of maximum percent reduction in the SPD will be created by treatment arm. These plots will display the best percentage change from baseline in the SPD of lymph nodes and extranodal sites for each patient with at least one adequate baseline and one post-baseline assessment.

#### 6.2.2.2. Disease Control

Disease Control (DC) is defined as BOR of CR, PR, or SD. DC rate (DCR) is the proportion of patients with DC.

DCR will be summarized by frequency counts and percentages.

#### 6.2.2.3. Duration of Response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are as described for PFS in Table 3.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rate at 3, 6, 9, 12 and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

#### 6.2.2.4. 6-month Durable Response

The 6-month DRR for each treatment arm will be estimated by dividing the number of patients who achieve and maintain an objective response for at least 6 months by the total number of patients randomized to the respective treatment arm.

The corresponding exact 2-sided 95% CIs will be provided by treatment arm using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

#### 6.2.2.5. Time to Response

Time to response (TTR) is defined, for patients with OR, as the time from the date of randomization to the first documentation of objective response (CR or PR).

TTR (in months) = [first date of OR – date of randomization +1]/30.4375.

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

#### 6.2.2.6. Progression-free Survival

Progression-Free Survival (PFS) is defined as the time from the date of randomization to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing or inadequate post-baseline tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the date of randomization unless death occurred on or before the time of the second planned tumor assessment (ie, ≤24 weeks after the date of randomization) in which case the death will be considered an event.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 12 (±1) weeks until PD regardless of initiation of subsequent anti-cancer therapy. After 12 months from date of randomization, tumor assessments will be conducted less frequently, ie, at 26-week (6-month) intervals.

The censoring and event date options to be considered for the PFS and DR analysis are presented in Table 4.

PFS (months) = [date of event or censoring– date of randomization +1]/30.4375.

**Table 4. Outcome and Event Dates for PFS and DR Analyses**

| Scenario | Date of event/censoring | Outcome |
|---|---|---|
| No adequate baseline assessment | Date of randomization[a] | Censored[a] |
| PD or death<br>- After at most one missing or inadequate post-baseline tumor assessment, OR<br>- ≤24 weeks after the date of randomization. | Date of PD or death | Event |
| PD or death<br>- after 2 or more missing or inadequate post-baseline tumor assessments. | Date of last adequate tumor assessment[b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments. | Censored |
| No PD and no death. | Date of last adequate tumor assessment[b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments. | Censored |
| Treatment discontinuation due to 'Disease progression' without documented progression. | Not applicable | Information is ignored. Outcome is derived based on documented progression only. |
| New anti-cancer therapy given. | Date of last adequate tumor assessment[b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments. | Censored |

[a] However if the patient dies ≤24 weeks after the date of randomization the death is an event with date on death date.
[b] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of randomization; if the criteria were met the censoring will be on the date of randomization.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rate at 3, 6, 9, 12 and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to the categories in Table 5 following the hierarchy shown.

**Table 5. PFS Censoring Reasons and Hierarchy**

| Hierarchy | Condition | Censoring Reason |
|---|---|---|
| 1 | No adequate baseline assessment | No adequate baseline assessment |
| 2 | Start of new anti-cancer therapy. | Start of new anti-cancer therapy |
| 3 | Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization | Event after missing assessments [a] |
| 4 | No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Subject refused further follow-up] | Withdrawal of consent |
| 5 | No event and lost to follow-up in any disposition page | Lost to follow-up |
| 6 | No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment | No adequate post-baseline tumor assessment |
| 7 | No event and none of the conditions in the prior hierarchy are met | Ongoing without an event |

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

**Time of Follow-Up for PFS**

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment arm. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment arms reversing the PFS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median time of follow-up for PFS with 2-sided 95% CIs. In particular, the rate at 3, 6, 9, 12 and 18 months will be estimated with corresponding 2-sided 95% CI.

### 6.2.2.7. Progression-free Survival at 6 Months

A patient will be considered to be progression-free at 6 months, if the patient has a disease assessment demonstrating non-progression for at least 6 months after randomization.

The PFS rate at 6 months for each treatment arm will be estimated by dividing the number of patients who are alive and progression-free at 6 months by the total number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

#### 6.2.2.8. Overall Survival

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– date of randomization +1]/30.4375.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rate at 6, 12, 18, 24 and 30 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to the categories in Table 6 following the hierarchy shown.

**Table 6. OS Censoring Reasons and Hierarchy**

| Hierarchy | Condition | Censoring Reason |
|---|---|---|
| 1 | No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Subject refused further follow-up] | Withdrawal of consent |
| 2 | No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date >10 weeks] | Lost to follow-up |
| 3 | No event and none of the conditions in the prior hierarchy are met | Alive |

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

#### Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment arms reversing the OS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median time of follow-up for OS with 2-sided 95% CIs. In particular, the rate at 6, 12, 18, 24 and 30 months will be estimated with corresponding 2-sided 95% CI.

### 6.2.3. Pharmacokinetic Endpoints

The following pharmacokinetic analyses will be presented by analyte and treatment arm based on the PK analyses set.

$C_{trough}$ and $C_{max}$ for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment arm, cycle, and day. Additional parameters may also be calculated as appropriate and as data permit, including, but not limited to:

- Following Single Dose (SD): $T_{max}$, $AUC_{last}$, $T_{last}$, $AUC_{sd,\tau}$, $AUC_{sd,inf}$, $t_{1/2}$, CL or CL/F, and $V_z$ or $V_z$/F.

- Following Multiple Dose (MD): $T_{ss,max}$, $AUC_{last}$, $T_{last}$, $AUC_{ss,\tau}$, $C_{ss,max}$, $t_{1/2}$, $C_{ss,av}$, CL or CL/F, $V_z$ or $V_z$/F, and $R_{ac}$ ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$).

Pharmacokinetic parameters for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be taken from observed values or derived from serum or plasma concentration-time data as described in Section 3.2.3.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of serum or plasma concentrations will be presented in tabular form by treatment arm, cycle, day and nominal time.

- Linear-linear and log-linear plots of mean and median serum or plasma concentrations by nominal time for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be presented for PK sampling days by treatment arm, cycle, and study day. Similar plots will be presented for each individual patient's concentrations. Patients who have undergone intrapatient dose reduction or escalation will be excluded from the median serum or plasma concentration-time plots.

- Pharmacokinetic parameters for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be listed and summarized by treatment arm, cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). $T_{max}$ will only be summarized with n, median, minimum, and maximum. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. If an intrapatient dose escalation or reduction occurs, data from this patient will only be included in descriptive statistics and summary plots up to the time of the dose change.

- Box plots for AUC and $C_{max}$ in Cycle 1 for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be generated. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment arm has limited evaluable PK data (n<4), matchstick plots showing changes in AUC and $C_{max}$ for each drug in individual patients will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots. For the analytes administered in 2 (rituximab, utomilumab) or 3 (avelumab) treatment arms and for analytes with more than 1 dosing day in a Cycle (azacitidine, bendamustine), data will be plotted for each treatment arm on the same

figure by cycle and dosing day. $C_{trough}$ and $C_{max}$ / $C_{ss, max}$ (if applicable) for avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite will be plotted for each treatment arm using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

### 6.2.4. Population Pharmacokinetic Endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab, rituximab, utomilumab, azacitidine, bendamustine and its M3 metabolite exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

### 6.2.5. Endpoints for Immunogenicity Data of Avelumab, Rituximab and Utomilumab

All analyses described below will be performed by treatment arm for each study drug.

All samples for ADA and nAb analyses for avelumab (3.5 mL), rituximab (4.0 mL) and utomilumab (4.0 mL) will be collected within 2 hours prior to the start of dosing on Day 1 in Cycle 1 (rituximab), Day 2 in Cycle 1 (avelumab and utomilumab) and Day 1 in Cycles 4 and 6 (rituximab, avelumab and utomilumab). Additional samples for immunogenicity analysis will be collected at 30 (±3) days after the end of therapy. A sample for ADA analysis will be drawn at the time of early withdrawal/treatment discontinuation.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb.

As of the finalization of this SAP, the nAb assay for avelumab is not yet available, therefore the analyses of avelumab nAb data described in the following sections will only be conducted contingent upon assay and data availability at the time of reporting.

Patients will be characterized into different ADA categories based on the criteria defined in Table 7.

**Table 7. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)**

| Category | Definition | Subjects at Risk (Denominator for Incidence) |
|---|---|---|
| ADA never-positive | No positive ADA results at any time point; ADA-negative patients (titer < cutpoint). | Number of patients with at least one valid ADA result at any time point. |
| ADA ever-positive | At least one positive ADA result at any timepoint, ADA-positive patients (titer ≥ cutpoint). | Number of patients with at least one valid ADA result at any time point. |
| Baseline ADA positive | A positive ADA result at baseline. | Number of patients with valid baseline ADA result. |
| Treatment-boosted ADA | A positive ADA result at baseline and the titer ≥8×baseline titer at least once after treatment with avelumab. | Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result. |
| Treatment-induced ADA | Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the | Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result |

| Category | Definition | Subjects at Risk (Denominator for Incidence) |
|---|---|---|
| | patient has at least one positive past-baseline ADA result. | (including missing, NR). |
| Transient ADA response | If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive. | Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR). |
| Persistent ADA response | If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment. | Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR). |

ADA: anti-drug antibody, NR = not reportable.

Patients will be characterized into different nAb categories based on the criteria in Table 8. For nAb, treatment-boosted is not applicable since no titer result is available.

**Table 8. Patients Characterized Based on Neutralizing Antibody Results (nAb Status)**

| Category | Definition | Subjects at Risk (Denominator for Incidence) |
|---|---|---|
| nAb never-positive | No positive nAb results at any time point | Number of patients with at least one valid ADA result at any time point. |
| nAb ever-positive | At least one positive nAb result at any time point | Number of patients with at least one valid ADA result at any time point. |
| Baseline nAb positive | A positive nAb result at baseline | Number of patients with valid baseline ADA result. |
| Treatment-induced nAb | Patient is not nAb positive at baseline and has at least one positive post-baseline nAb result; or if patient does not have a baseline sample, the patient has at least one positive past-baseline ADA result. | Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR). |
| Transient nAb response | If patients with treatment-induced nAb have (a single positive nAb result or duration between first and last positive result <16 weeks) and nAb result at the last assessment is not positive. | Number of patients with at least one ADA valid post-baseline result and without positive baseline nAb result (including missing, NR). |
| Persistent nAb response | If patients with treatment-induced nAb have duration between first and last positive nAb result ≥16 weeks or a positive nAb result at the last assessment. | Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR). |

ADA = antidrug antibody, nAb = neutralizing antibody, NR = no result.

The number and percentage of patients in each ADA and nAb category will be summarized.

#### 6.2.5.1. Time to and Duration of ADA and nAb Response

The ADA and nAb analyses described below will include patients with treatment-induced ADA or nAb, respectively.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of study drug + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- The last ADA assessment is positive AND patient is ongoing treatment with study drug, or
- The last ADA assessment is positive AND patient discontinued treatment with study drug, AND the last planned ADA assessment (day 30 follow-up visit) is after the cut-off date.

Time to nAb response and duration of nAb response are defined similarly based on first and last positive nAb result.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2011) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of ADA response will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with ADA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

As data permit, the analyses described above will be repeated for patients with treatment-induced nAb.

### 6.2.5.2. ADA Titer

For patients who are ADA ever positive, the maximum observed ADA titer for a patient will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of patients having each discrete maximum titer value. The denominator to calculate the percentages will be the total number of patients in the associated ADA subcategory.

For patients with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

### 6.2.5.3. Analysis of PK, Safety and Efficacy by Immunogenicity Status

The following ADA and nAb status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive.
- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive nAb.
- nAb ever-positive versus nAb never-positive.
- nAb: treatment-induced nAb versus nAb never-positive or baseline nAb positive.

Data listings will include immunogenicity data together with relevant PK, safety and efficacy data.

PK parameters and immunogenicity status

The effect of ADA on avelumab, utomilumab and rituximab concentrations will be evaluated. The following analyses will include patients in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoint pertinent to the immunogenicity analyses is $C_{trough}$.

$C_{trough}$ will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time and ADA status. Linear-linear and log-linear plots of mean and median for $C_{trough}$ over nominal time and by ADA status will be presented.

As data permit, the analyses described above will be repeated for nAb. This analysis will only be performed if nAb assays are available for all 3 biologics, including avelumab.

Safety and immunogenicity status

The following analyses will include patients in the immunogenicity analysis set.

The frequency (number and percentage) of patients with each of the following will be presented by ADA status.

- TEAEs, by SOC and PT.
- TEAEs leading to dose reduction of avelumab, by SOC and PT.
- TEAEs leading to dose reduction of rituximab, by SOC and PT.
- TEAEs leading to dose reduction of utomilumab, by SOC and PT.
- TEAEs leading to discontinuation of avelumab, by SOC and PT.
- TEAEs leading to discontinuation of rituximab, by SOC and PT.
- TEAEs leading to discontinuation of utomilumab, by SOC and PT.
- TEAEs leading to discontinuation of study treatment by SOC and PT.
- Grade ≥3 TEAEs, by SOC and PT.
- SAEs, by SOC and PT.
- IRRs, by PT.

For patients who had at least one IRR and have treatment-induced ADA, time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be summarized taking into account whether the IRR occurred on or after the first ADA positive assessment or whether the IRR occurred before the first ADA positive assessment.

As data permit, the analyses described above will be repeated for nAb. This analysis will only be performed if nAb assays are available for all 3 biologics, including avelumab.

Efficacy and immunogenicity status

For the ADA ever-positive patients, a listing will be prepared with patient ID, start and stop of avelumab treatment, date of first positive ADA result, time to ADA response, duration of ADA response, date of last ADA positive result, BOR, DR, PFS time or censoring time and reason for censoring, and OS time or censoring time and reason for censoring. If applicable, date of first positive nAb result, time to nAb response, duration of nAb response, date of last nAb positive result will also be presented. Tumor-related endpoints will be presented based on Investigator assessment.

For the ADA ever-positive patients, the percent change from baseline in target lesions as well as the first occurrence of a new lesion and patient off avelumab treatment will be displayed against time point (weeks) in a line plot. Additional symbols will indicate the first and last ADA positive result and, if applicable, the first and last nAb positive result. Plot will be presented based on Investigator assessment.

### 6.2.6. Analysis of PD-L1 and MRD

The following biomarker analyses will be based on the biomarker analysis set by treatment arm:

- PD-L1 expression will be reported by intensity score (0, +1, +2, +3) and percent of neoplastic cells expressing PD-L1 at each intensity score. The sum of percents of neoplastic cells presenting at +1 or greater scores will be reported as the percent of PD-L1 positive neoplastic cells. PD-L1 expression by inflammatory cells will be reported by intensity score (0, +1, +2, +3) and location (cytoplasmic, membrane, or both).

- CD8 expression (positive/negative) as determined by pathologist review will be reported as percent of cells or as cells per $mm^2$ scored as CD8-positive in the region of interest. Regions of interest are defined by the tumor mass as determined by pathologist review: ALL, all tumor areas within the tumor mass; invasive margin (IM), tumor mass and adjacent tissues measured from the edge of the tumor at approximately 500 μm into the tumor mass and adjacent tissues; PD-L1-positive center of tumor (CT+), PD-L1 positive regions of the tumor mass excluding IM; PD-L1-negative center of tumor (CT-), PD-L1-negative regions of the tumor mass excluding IM.

PD-L1 and CD8 expression values will be summarized descriptively as appropriate (n, mean, SD, CV, median, minimum, maximum, geometric mean, associated CV, and 95% CI) by treatment arm, and time-point, including baseline assessments. Values will be plotted for each treatment arm and time-point using a box-whisker plot in order to assess changes from baseline.

Correlations between PD-L1 and CD8 expression values (at baseline and on-treatment) and selected efficacy endpoints will be assessed retrospectively.

MRD status will be summarized descriptively as appropriate (n, positive/negative status, mean, SD, CV, median, minimum, maximum, geometric mean, associated CV, and 95% CI) by treatment arm, and time-point, including baseline assessments. Correlations between MRD assessed qualitatively (positive/negative) and/or quantitatively (at baseline and on-treatment) and selected efficacy endpoints will be assessed retrospectively.

CCI

CCI

CCI

CCI

## 6.4. Subset Analyses

Subset analyses are not planned.

## 6.5. Baseline and Other Summaries and Analyses

### 6.5.1. Baseline Summaries

The following analyses will be based on the FAS overall and separately by treatment arm.

#### 6.5.1.1. Demographic Characteristics

Demographic characteristics and physical measurements will be summarized by treatment arm using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics:
  - Gender: Male, Female.
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown.
  - Ethnic origin: Hispanic/Latino (Yes/No).
  - Age (years): summary statistics.
  - Age categories:
    - <65 years, ≥65 years.
    - < 65, 65-<75, 75-<85, ≥85 years.
  - Pooled Geographical Region (as applicable):
    - North America.
    - Europe.
    - Asia.
    - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including >10% of the overall randomized population).
  - Geographic Region (as applicable):
    - North America.
    - Latin America.
    - Western Europe.
    - Eastern Europe.

    - Middle East.
    - Australasia.
    - Asia.
    - Africa.
  - Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4.
- Physical measurements:
  - Height (cm).
  - Weight (kg).
  - Body Mass Index (BMI) ($kg/m^2$).
  - Body Surface Area (BSA) ($m^2$).

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment arm, age, sex, race, ethnicity, height (cm), weight (kg), BMI ($kg/m^2$), BSA ($m^2$) and ECOG performance status.

#### 6.5.1.2. Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

#### 6.5.1.3. Disease Characteristics

Information on disease characteristics collected on 'Primary Diagnosis', 'Substance Abuse' and Tumor Assessment eCRF pages will be summarized overall and by treatment arm. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor.

- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page).
- Time since initial diagnosis to date of randomization (months), defined as (date of randomization – date of initial diagnosis)/30.4375.
- Initial histopathological classification (including sub-category).
- Classification based on molecular profiling.
- Stage and substage at initial diagnosis.
- Time since most recent recurrence/progression (months), defined as (date of randomization – date of most recent recurrence/progression)/30.4375.
- Primary disease type (Refractory vs Relapsed).
- Stage and substage at current diagnosis.

From the Tumor Assessment eCRF pages:

- Involved tumor sites at baseline

From the 'Substance Use' eCRF page:

- Smoking history.
    - Never smoker vs current vs former smoker.
    - Smoking exposure (pack-years): 0, <20, 20-<40, ≥40 and summary statistics.
    - Years since quitting: never smoker, current smoker, <5, 5-<10, ≥10 and summary statistics.

    Specifications for computation:

- Cigarette equivalents are calculated as follows: one cigar is regarded equivalent to 5 cigarettes and 1 pipe is regarded equivalent to 3 cigarettes.
- Duration of nicotine consumption [years]:

    (end of nicotine consumption – start of nicotine consumption + 1) / 365.25.

- Pack-years:
    - Calculate cigarette equivalents per day using the conversion factors given above.
    - Convert to packs per day where 20 cigarettes are regarded as 1 pack.

- Pack-years = packs per day × duration of nicotine consumption [years]

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' and 'Substance Use' eCRF pages) and derived variables as above.

#### 6.5.1.4. Prior Anti-Cancer Therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer therapy.
- Patients with at least one prior anti-cancer drug therapy.
- Patients with at least one prior anti-cancer radiotherapy.
- Patients with at least one prior anti-cancer surgery.

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy.
- Number of prior anti-cancer drug therapy regimens: missing / 1 / 2 / 3 / ≥4.
- Prior anti-cancer immune therapy (including PD-1, PD-L1, anti-CTLA4, others).
- Best response: CR, PR, SD, PD, Unknown, Not Applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drug therapies will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies.
- Listing of anti-cancer radiotherapy.

- Listing of anti-cancer surgeries.

### 6.5.2. Study Conduct and Patient Disposition

The following analyses will be performed based on the FAS overall and separately by treatment arm.

#### 6.5.2.1. Patient Disposition

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall.
- Number of patients who discontinued from the study prior to randomization overall and by the main reason for discontinuation.
- Number and percentage of randomized patients in each of the analysis sets defined in Section 4.
- Number and percentage of randomized patients with study drug ongoing (separately for each study drug administered in combination).
- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination).
- Number and percentage of patients who entered follow-up.
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation.
- Number and percentage of patients who entered long-term follow-up.
- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation.

The results of the randomization algorithm (according to IRT) will be summarized as follows:

- Number and percentage of randomized patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region.
- Number and percentage of randomized patients by center.
- Cross tabulation: patients randomized (Arm A/Arm B/Arm C/none) vs. patients treated (Arm A/Arm B/Arm C/none).

#### 6.5.2.2. Protocol Deviations

All protocol violations that impact the safety of the patients and/or the conduct of the study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria or satisfying exclusion criteria.
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn.
- Patients who receive the wrong treatment or an incorrect dose.
- Patients who receive an excluded concomitant medication.
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

### 6.5.3. Study Treatment Compliance and Exposure

The following analyses will be based on the safety analysis set by treatment arm.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is:

- The earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose >0 at that visit).
- The first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- For all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- For the last cycle, actual cycle end date = actual cycle start date + 28 (in days) – 1 day.

**Cycle duration** (weeks) = (actual cycle end date – actual cycle start date + 1)/7.

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized (per cycle and/or overall) as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (eg, infusion cyclical).

The derivations below are provided for the following with 1 cycle = 4 weeks.

- Avelumab administered as a 1-hour IV infusion at a dose of 10 mg/kg once every 2 weeks in 4-week cycles.

  Avelumab is administered on Day 2 and Day 16 in Cycle 1 and Cycle 2. If avelumab is well tolerated in Cycle 1 and Cycle 2, then it will be administered on Day 1 and Day 15 of Cycle 3 and all subsequent cycles until the patient no longer receives clinical benefit.

- Utomilumab administered as an IV infusion at a fixed dose of 100 mg once every 4 weeks in 4-week cycles.

  Utomilumab is administered on the morning of Day 2 in Cycles 1 and 2. If utomilumab is well-tolerated in Cycles 1 and 2, then it will be administered on Day 1 in Cycle 3 and all subsequent cycles until the patient no longer receives clinical benefit.

- Rituximab administered as in IV infusion at a dose of 375 mg/$m^2$ once (on Day 1) every 4 weeks in 4-week cycles for up to 8 cycles.

- Bendamustine administered as in IV infusion at a dose of 90 mg/$m^2$ on Days 1 and 2 or Days 2 and 3 of each 4-week cycle for up to 6 cycles.

  Bendamustine is administered on Days 2 and 3 in Cycle 1 and Cycle 2. If bendamustine is well-tolerated in Cycle 1 and 2, then bendamustine may be administered on Days 1 and 2 in Cycle 3 and all subsequent cycles for up to 6 cycles.

- Azacitidine administered as a SC injection at a dose of 40 mg/$m^2$ from Day 1 to Day 5 of each 4-week cycle.

#### 6.5.3.1. Exposure to Avelumab

The dose level for avelumab is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

**Intended duration of treatment with avelumab** (weeks) =

(end date–date of first dose of avelumab +1)/7,

where end date = start date of last cycle with non-zero dose of avelumab + 28.

**Duration of exposure to avelumab** (weeks) =

(last dose date of avelumab – first dose date of avelumab + 14)/7.

**Cumulative dose** in a cycle or overall is the sum of the actual doses of avelumab received in a cycle or overall, respectively.

**Actual Dose Intensity (DI)**

- By cycle actual DI (mg/kg/4-week cycle) = [cumulative dose in the cycle (mg/kg)]/[cycle duration (weeks)/4].
- Overall actual DI (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with avelumab (weeks)/4].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/kg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [20 (mg/kg)] / [1 (4-week cycle)] = 20 (mg/kg/4-week cycle).
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [20 (mg/kg/4-week cycle)].
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [20 (mg/kg/4-week cycle)].

#### 6.5.3.2. Exposure to Utomilumab

The dose level for utomilumab is fixed (mg).

**Intended duration of treatment with utomilumab** (weeks) =

(end date–date of first dose of utomilumab +1)/7.

where end date = start date of last cycle with non-zero dose of utomilumab + 28.

**Duration of exposure to utomilumab** (weeks) =

(last dose date of utomilumab – first dose date of utomilumab + 28)/7.

**Cumulative dose** in a cycle or overall is the sum of the actual doses of utomilumab received in a cycle or overall, respectively.

**Actual Dose Intensity (DI)**

- By cycle actual DI (mg/4-week cycle) = [cumulative dose in the cycle (mg)]/[cycle duration (weeks)/4].

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with utomilumab (weeks)/4].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [100 (mg)] / [1 (4-week cycle)] = 100 (mg/4-week cycle).

- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [100 (mg/4-week cycle)].

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [100 (mg/4-week cycle)].

### 6.5.3.3. Exposure to Rituximab

The dose level for rituximab is calculated as actual dose administered/BSA (mg/m$^2$). The last available BSA of the patient on or prior to the day of dosing will be used.

**Intended duration of treatment with rituximab** (weeks) =

(end date–date of first dose of rituximab +1)/7,

where end date = start date of last cycle with non-zero dose of rituximab + 28 – 1.

**Duration of exposure to rituximab** (weeks) =

(last dose date of rituximab – first dose date of rituximab + 28)/7.

**Cumulative dose** in a cycle or overall is the sum of the actual doses of rituximab received in a cycle or overall, respectively.

**Actual Dose Intensity (DI)**

- By cycle actual DI (mg/m$^2$/4-week cycle) = [cumulative dose in the cycle (mg/m$^2$)]/[cycle duration (weeks)/4].

- Overall actual DI (mg/m$^2$/4-week cycle) = [overall cumulative dose (mg/m$^2$)] / [intended duration of treatment with rituximab (weeks)/4].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/$m^2$/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [375 (mg/$m^2$)] / [1 (4-week cycle)] = 375 (mg/$m^2$/4-week cycle).

- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [375 (mg/$m^2$/4-week cycle)].

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [375 (mg/$m^2$/4-week cycle)].

### 6.5.3.4. Exposure to Bendamustine

The dose level for bendamustine is calculated as actual dose administered/BSA (mg/$m^2$). The last available BSA of the patient on or prior to the day of dosing will be used.

**Intended duration of treatment with bendamustine** (weeks) =

(end date–date of first dose of bendamustine +1)/7,

where end date = start date of last cycle with non-zero dose of bendamustine + 28.

**Duration of exposure to bendamustine** (weeks) =

(last dose date of bendamustine – first dose date of bendamustine + d)/7,

where d=1 if the patient discontinues bendamustine prior to the 2 days of planned dosing in the last cycle or d=27 otherwise.

**Cumulative dose** in a cycle or overall is the sum of the actual doses of bendamustine received in a cycle or overall, respectively.

**Actual Dose Intensity (DI)**

- By cycle actual DI (mg/$m^2$/4-week cycle) = [cumulative dose in the cycle (mg/$m^2$)]/[cycle duration (weeks)/4].

- Overall actual DI (mg/$m^2$/4-week cycle) = [overall cumulative dose (mg/$m^2$)] / [intended duration of treatment with bendamustine (weeks)/4].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/$m^2$/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [180 (mg/$m^2$)] / [1 (4-week cycle)] = 180 (mg/$m^2$/4-week cycle).

- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [180 (mg/$m^2$/4-week cycle)].

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [180 (mg/m$^2$/4-week cycle)].

#### 6.5.3.5. Exposure to Azacitidine

The dose level for azacitidine is calculated as actual dose administered/BSA (mg/m$^2$). The last available BSA of the patient on or prior to the day of dosing will be used.

**Intended duration of treatment with azacitidine** (weeks) =

(end date–date of first dose of azacitidine +1)/7,

where end date = start date of last cycle with non-zero dose of azacitidine + 28 – 1.

**Duration of exposure to azacitidine** (weeks) =

(last dose date of azacitidine – first dose date of azacitidine + d)/7,

where d=1 if the patient discontinues azacitidine prior to the 5 days of planned dosing in the last cycle or d=24 otherwise.

**Cumulative dose** in a cycle or overall is the sum of the actual doses of azacitidine received in a cycle or overall, respectively.

**Actual Dose Intensity (DI)**

- By cycle actual DI (mg/m$^2$/4-week cycle) = [cumulative dose in the cycle (mg/m$^2$)]/[cycle duration (weeks)/4].

- Overall actual DI (mg/m$^2$/4-week cycle) = [overall cumulative dose (mg/m$^2$)] / [intended duration of treatment with azacitidine (weeks)/4].

**Relative Dose Intensity (RDI)**

- Intended DI (mg/m$^2$/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [200 (mg/m$^2$)] / [1 (4-week cycle)] = 200 (mg/m$^2$/4-week cycle).

- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [200 (mg/m$^2$/4-week cycle)].

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [200 (mg/m$^2$/4-week cycle)].

#### 6.5.3.6. Dose Reductions

Applicable to avelumab, utomilumab, azacitidine, bendamustine and rituximab. Dose reduction is defined as actual non-zero dose <90% of the planned dose.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

### 6.5.3.7. Dose Interruptions

Applicable to azacitidine and bendamustine.

An interruption is defined as a 0 mg/m$^2$ dose administered on one or more days. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (example: If the actual dose for azacitidine on days 1-3 is 40 mg/m$^2$ and actual dose on days 4-5 is 0 mg/m$^2$, and dose is administered again on days 6 and 7, and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1).

- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (example: If the actual dose for azacitidine on days 1-3 is 40 mg/m$^2$ and actual dose on days 4-5 is 0 mg/m$^2$, and dose is administered again on days 6 and 7, and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2).

- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, ie, there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is 40 mg/m$^2$ and actual dose on days 2 and 4 is 0 mg/m$^2$, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of patients with dose interruptions and the corresponding reasons will be summarized.

### 6.5.3.8. Dose Delays

**Avelumab**

Dose delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

For the first dose of Cycle 1

Dose Delay (days) = day of first dose of avelumab – 2.

After the first dose of Cycle 1

Dose Delay (days) = Date of dose x – Date of dose (x-1) – d, where d = 13 for the first dose of Cycle 3 and d = 14 for all others.

**Utomilumab**

Dose delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

In Cycle 1,

Dose Delay (days) = day of first dose of utomilumab – 2.

In Cycle >1

Dose Delay (days) = Date of first dose of utomilumab in Cycle x – Date of first dose of utomilumab in Cycle (x-1) – d, where d = 27 if x = 3 and d=28 if x = 2 or x ≥4.

**Rituximab**

Dose delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

In Cycle 1,

Dose Delay for Dose 1 (days) = day of first dose of rituximab in Cycle 1 – 1.

In Cycle >1

Dose Delay for Dose x (days) = Date of first dose of rituximab in Cycle x – Date of first dose of rituximab in Cycle (x-1) – 28.

**Bendamustine**

Dose delay is the difference between the actual time between the last non-zero dose of a cycle and the actual first non-zero dose of the next cycle and the planned time between the same two doses. Dose delay is only calculated for the first dose of bendamustine administered in each cycle.

In Cycle 1,

Dose Delay for Dose 1 (days) = day of first dose of bendamustine – 2.

In Cycle >1

Dose Delay (days) = Date of first dose of bendamustine in Cycle x – Date of first dose of bendamustine in Cycle (x-1) – d, where d = 27 if x = 3 and d=28 if x = 2 or x ≥4.

**Azacitidine**

Dose delay is the difference between the actual time between the last non-zero dose of a cycle and the actual first non-zero dose of the next cycle and the planned time between the same two doses. Dose delay is only calculated for the first dose of azacitidine administered in each cycle.

In Cycle 1,

Dose Delay for Dose 1 (days) = day of first dose of azacitidine – 1.

In Cycle >1

Dose Delay for Dose x (days) = Date of first dose of azacitidine in Cycle x – Date of first dose of azacitidine in Cycle (x-1) – 28.

Dose delays will be grouped into the following categories:

- No delay.
- 1-2 days delay.
- 3-6 days delay.
- 7 or more days delay.

For example, for avelumab, administered on a 2-week schedule, if one patient receives avelumab on Cycle 1 Day 2, then the next avelumab administration date will be on Cycle 1 Day 16; however, if the patient receives avelumab at Cycle 1 Day 17 or 18, this is considered as 1-2 days delay.

No delay and 1-2 days delay will also be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, the worst case of delay if patients have multiple dose delays will be summarized.

#### 6.5.3.9. Infusion Rate Reductions

Applicable to avelumab, utomilumab, rituximab, bendamustine.

The number and percentage of patients with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the eCRF as well as the frequency of patients with 1, 2, 3, or ≥4 infusion rate reductions of ≥50% will be summarized.

Infusion rate reductions are not applicable to azacitidine.

#### 6.5.3.10. Infusion Interruptions

Applicable to avelumab, utomilumab, rituximab, bendamustine.

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

Infusion interruptions are not applicable to azacitidine.

### 6.5.4. Concomitant Medications and Non-drug Treatments

The following analyses will be based on the safety analysis set by treatment arm.

**Concomitant medications** are medications, other than study medications, which started prior to first dose date of study treatment and continued on on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study medications and pre-medications for study drug, which are started before the first dose of study treatment.

Prior and concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page. Pre-medications for study drug will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, summary of concomitant medications and summary of pre-medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

### 6.5.5. Subsequent Anti-cancer Therapies

The following analyses will be based on the FAS by treatment arm.

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

### 6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment arm.

#### 6.6.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).

- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).

- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).

- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.

- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).

- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).

- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan and finalized for analysis of the current studies data prior to DB lock).

- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan and finalized for analysis of the current studies data prior to DB lock).

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment arm, primary SOC and PT in decreasing frequency based on the frequencies observed for Arm A.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

#### 6.6.1.1. All Adverse Events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following by treatment arm:
  - TEAEs.
  - TEAEs, Grade ≥3.
  - Related TEAEs.
  - Related TEAEs, Grade ≥3.
  - TEAEs leading to dose reduction of avelumab.
  - TEAEs leading to dose reduction of utomilumab.
  - TEAEs leading to dose reduction of rituximab.
  - TEAEs leading to dose reduction of bendamustine.
  - TEAEs leading to dose reduction of azacitidine.
  - TEAEs leading to interruption of avelumab.

- TEAEs leading to interruption of utomilumab.
- TEAEs leading to interruption of rituximab.
- TEAEs leading to interruption of bendamustine.
- TEAEs leading to interruption of azacitidine.
- TEAEs leading to discontinuation of avelumab.
- TEAEs leading to discontinuation of utomilumab.
- TEAEs leading to discontinuation of rituximab.
- TEAEs leading to discontinuation of bendamustine.
- TEAEs leading to discontinuation of azacitidine.
- TEAEs leading to discontinuation of any study drug.
- TEAEs leading to discontinuation of all study drugs.
- Related TEAEs leading to discontinuation of avelumab.
- Related TEAEs leading to discontinuation of utomilumab.
- Related TEAEs leading to discontinuation of rituximab.
- Related TEAEs leading to discontinuation of bendamustine.
- Related TEAEs leading to discontinuation of azacitidine.
- Related TEAEs leading to discontinuation of any study drug.
- Related TEAEs leading to discontinuation of all study drugs.
- Serious TEAEs.
- Related Serious TEAEs.
- TEAEs leading to death.
- Related TEAEs leading to death.
- irAEs.
- IRRs.

- TEAEs by SOC and PT and worst grade.
- Related TEAEs by SOC and PT and worst grade.
- TEAEs related to avelumab by SOC and PT and worst grade.
- TEAEs related to utomilumab by SOC and PT and worst grade.
- TEAEs related to rituximab by SOC and PT and worst grade.
- TEAEs related to bendamustine by SOC and PT and worst grade.
- TEAEs related to azacitidine by SOC and PT and worst grade.
- TEAEs related to any study drug by SOC and PT and worst grade.
- TEAEs leading to death by SOC and PT.
- Related TEAEs leading to death by SOC and PT.
- TEAEs Excluding SAEs, with frequency ≥5% in any treatment arm by SOC and PT.

#### 6.6.1.2. Adverse Events Leading to Dose Reduction

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to dose reduction of each study drug by treatment arm:

- TEAEs leading to dose reduction of avelumab by SOC and PT.
- TEAEs leading to dose reduction of utomilumab by SOC and PT.
- TEAEs leading to dose reduction of rituximab by SOC and PT.
- TEAEs leading to dose reduction of bendamustine by SOC and PT.
- TEAEs leading to dose reduction of azacitidine by SOC and PT.

The listing of all AEs leading to dose reduction will also be provided with the relevant information.

#### 6.6.1.3. Adverse Events Leading to Interruption of Study Treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF (“Drug interrupted”). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of ‘drug interrupted’ excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.6). These IRRs will be considered as IRRs leading to interruption of infusion.

- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.6).

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment arm:

- TEAEs leading to interruption of avelumab by SOC and PT.

- TEAEs leading to interruption of utomilumab by SOC and PT.

- TEAEs leading to interruption of rituximab by SOC and PT.

- TEAEs leading to interruption of bendamustine by SOC and PT.

- TEAEs leading to interruption of azacitidine by SOC and PT.

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

In addition, the frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment arm:

- TEAEs leading to both interruption and dose reduction of avelumab by SOC and PT.

- TEAEs leading to both interruption and dose reduction of utomilumab by SOC and PT.

- TEAEs leading to both interruption and dose reduction of rituximab by SOC and PT.

- TEAEs leading to both interruption and dose reduction of bendamustine by SOC and PT.

- TEAEs leading to both interruption and dose reduction of azacitidine by SOC and PT.

This summary will take into account PTs with both actions as defined in Section 6.6.1, eventhough the actions may be captured for different PT records (ie, different onset for the PT with action “drug interrupted” and the PT with action “dose reduced”.

#### 6.6.1.4. Adverse Events Leading to Discontinuation of Study Treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment arm:

- TEAEs leading to discontinuation of avelumab by SOC and PT.

- Related TEAEs leading to discontinuation of avelumab by SOC and PT.
- TEAEs leading to discontinuation of utomilumab by SOC and PT.
- TEAEs leading to discontinuation of rituximab by SOC and PT.
- TEAEs leading to discontinuation of bendamustine by SOC and PT.
- TEAEs leading to discontinuation of azacitidine by SOC and PT.
- Related TEAEs leading to discontinuation of utomilumab by SOC and PT.
- Related TEAEs leading to discontinuation of rituximab by SOC and PT.
- Related TEAEs leading to discontinuation of bendamustine by SOC and PT.
- Related TEAEs leading to discontinuation of azacitidine by SOC and PT.
- TEAEs leading to discontinuation of any study drug by SOC and PT.
- Related TEAEs leading to discontinuation of any study drug by SOC and PT.
- TEAEs leading to discontinuation of all study drugs by SOC and PT.
- Related TEAEs leading to discontinuation of all study drugs by SOC and PT.

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

### 6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment arm.

- All deaths.
- Deaths within 30 days after last dose of study treatment.
- Reason for Death.
    - Disease progression.
    - Study treatment toxicity.
    - AE not related to study treatment.
    - Unknown.

- Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5).
- Flag for death within 30 days of last dose of study treatment.

### 6.6.3. Serious Adverse Events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs by treatment arm:

- SAEs by SOC and PT.
- Related SAEs by SOC and PT.

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

### 6.6.4. Other Significant Adverse Events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs, by treatment arm:

- irAEs leading to death, by Cluster and PT.
- irAEs, by Cluster and PT.
- irAEs, Grade ≥3, by Cluster and PT.
- irAEs leading to discontinuation of avelumab, by Cluster and PT.
- irAEs leading to discontinuation of utomilumab, by Cluster and PT.
- irAEs leading to discontinuation of rituximab, by Cluster and PT.
- irAEs leading to discontinuation of bendamustine, by Cluster and PT.
- irAEs leading to discontinuation of azacitidine, by Cluster and PT.
- irAEs leading to discontinuation of any study drug, by Cluster and PT.
- irAEs leading to discontinuation of all study drugs, by Cluster and PT.
- Serious irAEs, by Cluster and PT.

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of patients with each of the following will be presented for IRRs, by treatment arm:

- IRRs leading to death, by PT.
- IRRs, by PT.
- IRRs, Grade ≥3, by PT.
- IRRs leading to discontinuation of avelumab, by PT.
- IRRs leading to discontinuation of utomilumab, by PT.
- IRRs leading to discontinuation of rituximab, by PT.
- IRRs leading to discontinuation of bendamustine, by PT.
- IRRs leading to discontinuation of azacitidine, by PT.
- IRRs leading to discontinuation of any study drug, by PT.
- IRRs leading to discontinuation of all study drugs, by PT.
- Serious IRRs, by PT.
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later). For IV study drugs administered in combination the infusion numbers are those associated with the regimen, rather than the individual study drugs.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

### 6.6.5. Laboratory Data

#### 6.6.5.1. Hematology and Chemistry Parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Quantitative data will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each

nominal visit over time (unscheduled measurements would therefore not be included in these summaries as described in Section 5.2.9). End of Treatment visit laboratory results will be summarized separately. The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (ie, Low, Normal, High).

Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥800/mm3.
- Neutrophil count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥1500/mm3.

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L]).

**Liver function tests**: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios

of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment arm:

- ALT ≥3×ULN, ALT ≥5×ULN, ALT ≥10×ULN, ALT ≥20×ULN.
- AST ≥3×ULN, AST ≥5×ULN, AST ≥10×ULN, AST ≥20×ULN.
- (ALT or AST) ≥3×ULN, (ALT or AST) ≥5×ULN, (ALT or AST) ≥10×ULN, (ALT or AST) ≥20×ULN.
- TBILI ≥2×ULN.
- Concurrent ALT ≥3×ULN and TBILI ≥2×ULN.
- Concurrent AST ≥3×ULN and TBILI ≥2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP >2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and (ALP ≤2×ULN or missing).

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment arms, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥2×ULN, ALT ≥3×ULN or AST ≥3×ULN will be provided.

**Parameters with NCI-CTC grades available:**

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie, those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of patients with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

**Parameters with NCI-CTC grades not available:**

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period.

- shifts from baseline normal to at least one result below normal during on-treatment period.

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils.
- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH).

#### 6.6.5.2. Other Laboratory Parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (INR).
- Urinalysis: all urinalysis parameters.
- Other parameters: hormone, viral serology and immunology parameters.
- Pregnancy test.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

### 6.6.6. Vital Signs

Weight for the purposes of dose calculation will be recorded on Day 1 and Day 15 of each cycle for the first 6 cycles, and on Day 1 only for cycles >6. Weight will also be collected at End of Treatment. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

### 6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

**Selecting Primary QT Correction for Heart Rate**

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of patients (eg, >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression methods which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data.
- Use the estimated slope, $\hat{b}$, to correct QT.
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} \times (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

**ECG Summaries**

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment arm, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments.
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point.
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms.
  - QT/QTc >450 ms, >480 ms, >500 ms.
  - HR ≤50 bpm and decrease from baseline ≥20 bpm.
  - HR ≥120 bpm and increase from baseline ≥20 bpm.
  - PR ≥220 ms and increase from baseline ≥20 ms.
  - QRS ≥120 ms.

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

### 6.6.8. MUGA/ECHO

LVEF% will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time. In addition, LVEF% will be summarized as frequency (number and percentage) of patients with:

- a shift from baseline normal to at least one result below the institutional lower limit of normal during the on-treatment period.
- ≥10-point decrease from baseline in LVEF% during the on-treatment period.
- ≥10-point decrease from baseline in LVEF% to a post-baseline value < LLN during the on-treatment period.
- ≥15-point decrease from baseline in LVEF%.
- ≥15-point decrease from baseline in LVEF% to a post-baseline value < LLN during the on-treatment period.

Clinically significant findings will be listed.

### 6.6.9. Physical Examination

Number and percentage of patients with abnormal findings in physical examination will be summarized by body system.

### 6.6.10. ECOG Performance Status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by treatment arm. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

## 7. INTERIM ANALYSES

See Section 5.1.2.

## 8. REFERENCES

1. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53: 457-81, 1958.

2. Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.

3. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38: 29-41, 1982.

4. Kalbfleisch JD, Prentice, RL. Statistical Analysis of Failure Time Data, 2nd Edition. Hoboken, Wiley Interscience

5. Cheson B, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014; 32:3059-68.

# 9. APPENDICES

## Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the Safety Review Plan (SRP) for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 9. This case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

**Table 9. Case Definition for irAEs**

| Step | Selection Criteria | Additional Notes |
|---|---|---|
| 1 | Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list then it is in for the next step | |
| 2 | AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment. | This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications |
| 3 | Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'. | |
| 4 | AE treated with corticosteroids or other immunosuppressant therapy.<br>For endocrinopathies only: AE required hormone replacement. | Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) below are met then the AE is in for the next step.<br>A) conmed ATC code is in (H02A, H02B, H02C, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters.<br>B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies".<br>C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus". |

| | | |
|---|---|---|
| 5 | A) No clear etiology (other than immune mediated etiology).<br><br>B) Histopathology / biopsy consistent with immune-mediated event.<br><br>Event is in if<br>[Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)].<br>OR<br>[Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO].<br>OR<br>[Answer to 5B1 is NO AND answer to 5A is NO]. | A) From the AE eCRF page<br>Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No<br>If answer is Yes, check all that apply:<br>• Underlying malignancy / progressive disease.<br>• Other medical conditions.<br>• Prior or concomitant medications / procedures.<br>• Other. Specify.<br><br>B) From the AE eCRF page<br>B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N<br>B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N<br>B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text). |

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

## Appendix 2. Infusion Related Reactions

For defining an AE as IRR the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.

- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 10 or Table 11 and will be identified for IV drugs only.

**Table 10. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs**

| Condition | Selection criterion |
|---|---|
| If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR. | |
| 1 | PT is included in the 'IRRs SIGNS and SYMPTOMS' list |
| 2 | • AE onset date = date of infusion of study drug, AND<br>• AE timing related to study drug ('DURING', 'AFTER'), AND<br>• AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING'), AND<br>• AE end date – AE onset date <=2. |
| 3 | PT is included in the 'IRRs CORE' list. |
| 4A | • AE onset date = date of infusion of study drug, AND<br>• AE timing related to study drug in ('DURING', 'AFTER'). |
| 4B | AE onset on the day after infusion. |

## Table 11. Case Definition for IRRs – IV Study Drugs Administered in Combination (eg, Doublets or Triplets)

| Condition | Selection criterion |
|---|---|
| IRR can be associated with the first IV drug and/or subsequent IV drugs that are administered in combination. Without loss of generality assume triplet IV with $D_1$ administered first then $D_2$ then $D_3$. The IV study drug or drugs associated with the IRR need to be identified in the analysis data set to enable subsequent analysis.<br><br>The following are not sequential and an AE can be classified as an IRR associated with multiple $D_J$ from one or more of I, II, III, IV, V below:<br><br>I - If the AE meets [1 AND 2A1] for a $D_J$ then the AE is classified as an IRR associated with the $D_J$ that meets the 2A1 criterion.<br><br>II - If the AE meets [1 AND 2A2] for a $D_J$ then the AE is classified as an IRR associated with the $D_J$ and associated with $D_{J+1}$ that meets the 2A2 criterion.<br><br>III - If the AE meets [3 AND 4B] for any $D_J$ then the AE is classified as an IRR associated with all $D_J$ that meet the 4B criterion.<br><br>IV- If the AE meets [3 AND 4A1] for a $D_J$ then the AE is classified as an IRR associated with the $D_J$ that meets the 4A1 criterion.<br><br>V- If the AE meets [3 AND 4A2] for a $D_J$ then the AE is classified as an IRR associated with the $D_J$ and associated with $D_{J+1}$ that meets the 4A2 criterion. | |
| 1 | PT is included in the 'IRRs SIGNS and SYMPTOMS' list |
| 2A1 | • AE onset date = date of infusion of study drug $D_J$, AND<br>• AE timing related to study drug $D_J$ ('DURING', 'AFTER'), AND<br>• [AE timing related to study drug $D_{J+1}$ ('BEFORE') OR AE onset date < date of infusion of study drug $D_{J+1}$], AND<br>• AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING'), AND<br>• AE end date – AE onset date <=2. |
| 2A2 | • AE onset date = date of infusion of study drug $D_J$, AND<br>• AE timing related to study drug $D_J$ ('DURING', 'AFTER'), AND<br>• AE timing related to study drug $D_{J+1}$ ('DURING', 'AFTER'), AND<br>• AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING'), AND<br>• AE end date – AE onset date <=2. |
| 3 | PT is included in the 'IRRs CORE' list. |
| 4A1 | • AE onset date = date of infusion of study drug $D_J$, AND<br>• AE timing related to study drug $D_J$ ('DURING', 'AFTER'), AND<br>• [AE timing related to study drug $D_{J+1}$ ('BEFORE') OR AE onset date < date of infusion of study drug $D_{J+1}$]. |

| | |
|---|---|
| 4A2 | • AE onset date = date of infusion of study drug $D_J$, AND<br>• AE timing related to study drug $D_J$ ('DURING', 'AFTER'), AND<br>• AE timing related to study drug $D_{J+1}$ ('DURING', 'AFTER'). |
| 4B | AE onset on the day after infusion of study drug $D_J$. |