STATISTICAL ANALYSIS PLAN

Protocol Number: MI-CP204

An Open-label, Phase 1/2 Study of MEDI-551, a Humanized Monoclonal Antibody Directed Against CD19, in Adult Subjects With Relapsed or Refractory Advanced B-Cell Malignancies

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1 INTRODUCTION

This document describes the statistical methodology and summaries for Study MI-CP204, an investigation of MEDI-551 in adult subjects with relapsed or refractory advanced B-cell malignancies. As background information, an overview of the study design is provided. The main portion of this document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used.

In addition, a set of table templates and specifications will be provided in a statistical programming plan to complement this document.

2 BACKGROUND

Cluster of Differentiation (CD) antigen 19 (CD19) is a B-cell-restricted transmembrane protein member of the immunoglobulin (Ig) superfamily encoded by the CD19 gene (Cooper et al, 2004). CD19 expression in B-cell leukemias and lymphomas is widespread. CD19 is expressed in chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), and B-cell non-Hodgkin's lymphoma (NHL) (Uckun et al, 1988; D'Arena et al, 2000; Ginaldi et al, 1998; Anderson et al, 1984).

Treatment of B-cell CLL and NHL, the largest groups of hematologic malignancies, relies primarily on a combination of chemotherapy and biotherapy based on the monoclonal antibody rituximab, directed against CD20 (Robak, 2007). While many patients achieve long-lasting remissions with this combination in both CLL and NHL, patients whose disease progresses after treatment with rituximab and/or commonly used chemotherapies have few effective options (Robak, 2007; Coiffier, September 2005; Coiffier, March 2005). With each subsequent treatment, the duration of remission usually becomes shorter and, eventually, most CLL and NHL patients die from their disease (Hennessy et al, 2004). Therefore patients who have relapsed or refractory NHL or CLL that is no longer responsive to rituximab or chemotherapy have an unmet medical need. The broad expression profile of CD19 on B-cell malignancies, including ALL, CLL, and NHL, makes this an attractive target both for patients in whom therapy with rituximab has failed and as a potential first-line treatment (Uckun et al, 1988). In multiple myeloma (MM), patients who are not candidates for a stem cell transplant (SCT) can achieve durable remissions with first-line chemotherapeutic regimens (San Miguel et al, 2008), but nearly all patients will eventually experience relapse and require subsequent therapy (Richardson et al, 2003). As with other B-cell malignancies, in MM, therapy with subsequent lines has a lower effectiveness and shorter duration (Richardson et al, 2003). MM patients who have received multiple lines of therapy likely have higher percentages of CD19-expressing cells (Matsui et al, 2008) and, because this may

represent a stem cell population that is resistant to available chemotherapies, these patients have an unmet medical need.

MEDI-551 is a humanized Immunoglobulin G (IgG)1 kappa monoclonal antibody (MAb) directed against human CD19. MEDI-551 efficiently depletes blood and tissue B cells in human CD19 transgenic (huCD19 Tg) mice and has antitumor activity in severe combined immunodeficiency (SCID) mouse models of human B cell leukemia, lymphoma and MM. MEDI-551 does not bind CD20, and thus activity of MEDI-551 should be independent of activity of rituximab or other CD20-targeted therapies. MEDI-551 is expected to selectively target B cells, with antitumor activity in a variety of B-cell-derived malignancies. More details on the clinical experience with MEDI-551 can be found in the Section 1.4 of the protocol.

2.1 Study Overview

This is a Phase 1/2, multicenter, international, open-label, dose-escalation and expanded cohort study to evaluate the safety, tolerability, and potential antitumor activity of MEDI-551 as single agent or in combination with rituximab in adult subjects with advanced B cell malignancies. The study design of Arm A comprises a dose-escalation phase followed by a dose-expansion phase in subjects with advanced B-cell malignancies receiving single-agent MEDI-551. This study arm included participants from 5 to 30 investigational sites in the United States (US), Canada, and European Union (EU). As of Version 10.0 of the protocol, the study design also includes dose escalation and expansion in subjects with CLL receiving single-agent MEDI-551 (Arm B), and dose escalation and expansion in subjects with aggressive lymphoma receiving MEDI-551 combined with rituximab (Arm C). As of Version 11.0 of the protocol, the study design also includes subjects with any anti-CD20-refractory aggressive lymphoma receiving single-agent MEDI-551 (Arm D). Arms B, C, and D will include participants from 20 investigational sites in the US and 10 to 15 sites in the EU.

Arm A

Enrollment in the dose-escalation and expansion phases of Arm A is complete. Protocol Version 4.0 was amended to make the study population for dose-escalation inclusive of subjects with FL, multiple myeloma (MM), CLL, or DLBCL. Dose escalation in Arm A began in subjects with FL or MM per protocol Versions 1.0 through 4.0. Subjects were enrolled into the first 2 cohorts under these versions of the protocol. Starting with Version 5.0 of the protocol, enrollment in dose-escalation Cohorts 3 and higher was open to subjects with the following advanced B-cell malignancies: FL, MM, CLL, or DLBCL. Subjects in Cohorts 1 and 2 were to continue to follow the protocol Version 4.0 dose schedule of 0.5

mg/kg (Cohort 1) or 1 mg/kg (Cohort 2) MEDI-551 administered intravenously (IV) once every week in 4-week cycles. Subjects enrolled in Cohorts 3 and higher received 2, 4, 8, or 12 mg/kg MEDI-551 (Cohorts 3 to 6, respectively) IV once per week on Days 1 and 8 of Cycle 1 (loading doses) and then once every 28 days at the start of each subsequent cycle. As per Cohorts 1 and 2, dosing in Cohorts 3 and higher followed a standard 3+3 dose-escalation scheme. Subjects in Arm A were not to receive a MEDI-551 dose greater than 12 mg/kg. No intra-subject dose escalation was allowed.

Arm B

Based on evaluation of the PK data in CLL subjects (n = 26) from Arm A, there appeared to be lack of full exposure and numerically lower response rate compared to non-CLL subjects using the current monthly dosing regimen at the highest dose evaluated (ie, 12 mg/kg). This arm of the study will evaluate further dose escalation in CLL subjects utilizing a new schema, designed to saturate the potential B-cell sink, achieve full exposure, and maximize clinical activity, by employing weekly dosing of MEDI-551 for 4 weeks during Cycle 1 and then monthly dosing on Day 1 of each subsequent 28-day cycle to determine the MTD or the highest protocol-defined dose in the absence of exceeding the MTD, which will be evaluated subsequently in a doseexpansion phase. To further minimize infusion related reactions at higher dose levels, for the 24 and 48 mg/kg dose levels of MEDI-551, the initial weekly dose will be administered over 2 days on Day 1 and Day 2 in Cycle 1. Subsequent doses at the 24 and 48 mg/kg dose levels will be administered in an identical fashion to lower dose levels (ie, weekly on Days 8, 15, and 22 in Cycle 1 and then on Day 1 of each 28-day cycle in Cycle 2 and beyond).

Arm C

Given the high unmet medical need in patients with multiply relapsed aggressive lymphoma, the synergistic activity observed in preclinical studies with MEDI-551 and rituximab, as well as the promising clinical activity seen with other dual monoclonal antibody (MAb) combinations in patients with B-cell malignancies, this arm of the study will evaluate the safety and efficacy of MEDI-551 in combination with rituximab in subjects with aggressive lymphoma (relapsed or refractory DLBCL, Grade 3b FL, FL transforming to DLBCL and mantle cell lymphoma [MCL]). Using a standard 3+3 design, 3 to 6 subjects with aggressive non-Hodgkin lymphoma (NHL) will be enrolled per cohort in the dose-escalation portion of this arm, starting at a MEDI-551 dose of 8 mg/kg and escalating to 12 mg/kg. This population will receive 8 mg/kg of MEDI-551 on Days 2 and 8 of Cycle 1 and Day 1 of Cycle 2, and beyond in 28-day cycles along with weekly rituximab for 8 weeks beginning on

Day 1 of Cycle 1. Dose escalation will continue to 12 mg/kg if 0 of 3 or ≤ 1 of 6 subjects treated at the lower dose experience a DLT. The MTD will be defined as the dose at which no more than 1 of 6 subjects experiences a DLT. No intrasubject dose escalation will be allowed. Subjects will be considered evaluable for a DLT if they complete the first cycle of therapy or discontinue therapy during Cycle 1 due to a DLT. Nonevaluable subjects will be replaced in the same dose cohort. A total of up to 12 subjects will be enrolled in the dose-escalation portion of this arm of the study. Dose escalation may be halted at the sponsor's discretion. Dose escalation will be permitted after all investigators review the available data and unanimously agree to proceed with enrollment into the next cohort. The outcome from this meeting will be documented in writing and shared with all participating sites. Once an MTD is identified or the maximum planned dose not exceeding the MTD is reached, additional subjects will be enrolled and treated at the selected dose of MEDI-551 in combination with rituximab in the dose-expansion portion of this arm to ensure a total sample size of 26 efficacy evaluable subjects are available for analysis after completing one post-treatment disease evaluation. The 26 subjects will include subjects treated at the selected dose during the dose-escalation portion of this arm. Treatment may continue until the subject experiences unacceptable toxicity, disease progression, or withdraws consent. Subjects in Arm C will be stratified by their responsiveness to any prior anti-CD20-based therapy with the option of ensuring a minimum number of 7 subjects who are refractory to any anti-CD20-based therapies are enrolled if clinical data from Arm D or emerging preclinical data suggest that the combination of anti-CD20 and anti-CD19 therapies improve response in this subpopulation.

Arm D

Given the high unmet medical need in patients with refractory aggressive lymphoma and in light of preservation of CD19 expression on the surface of these malignant cells, MEDI-551 may represent a salvage therapy option for anti-CD20-refractory patients. With evidence of clinical activity and safety of MEDI-551 established in an unselected relapsed refractory lymphoma population (Arm A), it is now appropriate to investigate MEDI-551 in the anti-CD20-refractory population. Arm D will evaluate the efficacy of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas (refractory DLBCL, Grade 3b FL, FL transforming to DLBCL, and MCL). Since the safety and tolerability of the 12-mg/kg dose of MEDI-551 has been verified in Arm A, approximately 26 subjects with any anti-CD20-refractory disease will be enrolled and treated with single-agent MEDI-551 at the dose and schedule used in the expansion cohort of Arm A (ie, 12 mg/kg of MEDI-551 on Days 1 and 8 of Cycle 1, and on Day 1 of Cycle 2 and beyond in 28-day cycles). Treatment may continue

until the subject experiences unacceptable toxicity, disease progression, or withdraws consent.

Primary Objectives:

Arm A (MEDI-551 monotherapy in advanced B-cell malignancies)

- To determine the maximum tolerated dose (MTD) or optimal biologic dose (OBD) of MEDI-551 in subjects with relapsed or refractory advanced B-cell malignancies (chronic lymphocytic leukemia [CLL], including small lymphocytic lymphoma [SLL], diffuse large B-cell lymphoma [DLBCL], and follicular lymphoma [FL])
- To determine the preliminary safety profile of MEDI-551

Arm B (MEDI-551 monotherapy in CLL)

Dose Escalation

- To determine the MTD or highest protocol-defined dose of MEDI-551 in the absence of exceeding the MTD in subjects with relapsed or rituximab-refractory CLL (defined as those with less than a partial response [PR] or progression within 6 months after completing therapy with rituximab)

Dose Expansion

- To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL
- To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in subjects with relapsed or rituximab-refractory CLL

Arm C (MEDI-551 combined with rituximab in aggressive lymphoma)

Dose Escalation

- To determine the safety and tolerability of MEDI-551 in combination with rituximab at the MTD or the highest protocol-defined dose in the absence of exceeding the MTD in subjects with aggressive lymphomas

Dose Expansion

- To evaluate further the safety and tolerability of MEDI-551 at the dose selected in the dose-escalation phase in subjects with aggressive lymphomas

- To evaluate the clinical activity of MEDI-551 at the dose selected in the dose-escalation phase in combination with rituximab in relapsed and rituximab-refractory population (defined as those with less than a PR or progression within 6 months after completing therapy with rituximab)

Arm D (MEDI-551 monotherapy in any anti-CD20-refractory aggressive lymphoma)

- To evaluate the clinical activity of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas (defined as any subject with less than a PR to any prior anti-CD20-based therapy or progression within 6 months after completing therapy with any anti-CD20-based regimen, including maintenance rituximab)

Secondary Objectives:

Arm A

- To determine the preliminary efficacy profile of MEDI-551 in subjects with advanced B-cell malignancies (CLL [including SLL], DLBCL, and FL)
- To determine the pharmacokinetics (PK) of MEDI-551 in subjects with advanced B-cell malignancies
- To determine the effect of treatment with MEDI-551 on circulating lymphocyte populations and immunoglobulin (Ig) levels, including time to recovery after treatment
- To determine the immunogenicity (IM) of MEDI-551 in subjects with advanced B-cell malignancies

Arm B

- To evaluate the PK and IM of MEDI-551 at doses studied in subjects with relapsed or rituximabrefractory CLL
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm C

- To evaluate the PK and IM of MEDI-551 when administered in combination with rituximab in subjects with aggressive lymphomas
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Arm D

- To determine the safety and tolerability of MEDI-551 in subjects with any anti-CD20-refractory aggressive lymphomas
- To evaluate the PK and IM of MEDI-551
- To evaluate the effect of therapy on the B-lymphocyte level in peripheral blood, including time to recovery of B-lymphocyte level

Exploratory Objectives:

Arm A

- [redacted]

Arm B

- [redacted]

Arm C

- [redacted]
- [redacted]

Arm D

- [redacted]
- [redacted]

2.2 Randomization and Blinding

This is an open-label study. Randomization and blinding are not applicable to this study.

2.3 Schedule of Study Procedures

The schedule of Study Procedures is outlined in the study protocol.

2.4 Sample Size Considerations

Arm A

For the dose-escalation phase, a minimum of 18 evaluable subjects (3 subjects each in Dose Cohort 1 through 6) or up to approximately 36 evaluable subjects (3+3 subjects per dose cohort) will be required to determine the MTD. A subject will be considered evaluable for assessment of DLT if the subject receives at least one full cycle (4 doses for Cohorts 1 and 2; 2 doses for Cohorts 3 to 6) of MEDI-551 and completes the safety follow-up through the DLT evaluation period (as defined in Section 4.5.6), or the subject experiences a DLT. Any nonevaluable subject will be replaced in the same dose cohort. Table 2.4-1 provides the probability of dose escalation to the next higher lever for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Table 2.4-1 True Underlying DLT Rate at a Given Dose Level

True Underlying DLT Rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

For the dose expansion phase, approximately 20 subjects will be entered into each of 4 arms to determine the preliminary efficacy profile of MEDI-551 in the treatment of advanced CLL, DLBCL, FL, and MM. The primary objective of the dose expansion phase is to determine the preliminary efficacy profile of MEDI-551 in subjects with the advanced B-cell malignancies, including CLL, DLBCL, FL, and MM. The sample size estimation is based on the exact binomial test. A total of 20 subjects will be required to have approximately 80% power for testing the following hypotheses at 1-sided significance level of 0.1.

- Null hypothesis: undesirable CR rate = 5%
- Alternative hypothesis: desirable CR rate = 20%

Arms B and C

Dose Escalation

There are 4 planned dose levels (6, 12, 24, and 48 mg/kg) for MEDI-551 in the Arm B dose escalation phase and 2 planned dose levels (8 and 12 mg/kg) for Arm C dose escalation. Using a standard 3+3 design, approximately 24 to 36 subjects may be enrolled during the dose-escalation phase in Arms B and C depending on the observed safety profile and total number of dose levels evaluated.

Dose Expansion

A sample size of 26 subjects is planned for each dose-expansion cohort in Arms B and C. Given an expected response rate of 50% for both cohorts, this will provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30%, and associated 80% confidence intervals for the response rate will have a precision of ± 13%. The 30% historical response rate was selected for both Arms B and C expansion cohorts based on the following reported data:

In relapsed CLL patients, OR rates between 15% and 30% were reported for rituximab monotherapy (O'Brien et al, 2001; Mavromatis and Cheson, 2003).

In DLBCL patients with 2 prior lines of therapy, response rates were only about 30% with single-agent rituximab (Coiffier et al, 1998; Wang et al, 2013; Churpek et al, 2013).

Arm D

A sample size of approximately 26 subjects is planned for Arm D. Given an expected response rate of 50% for this cohort, this will provide 80% power at a significance level of 0.20 (2-sided) to exclude the historical response rate of 30% (Zinzani et al, 2013; Witzig et al, 2011), and associated 80% confidence intervals for the response rate will have a precision of ± 13%.

3 STATISTICAL METHODS

3.1 General Considerations

All data will be provided in data listings sorted by dose level and subject number. All summary tables will be provided by dose level. The summary tables for baseline disease characteristics, study drug exposure, MTD evaluation and efficacy will be provided by dose level and disease type (CLL, DLBCL, FL, MM, MCL). Categorical data will be summarized

by frequency distribution (number and percentage of subjects falling within each category). In general, continuous variables will be summarized by descriptive statistics including N, mean, standard error or deviation, median, minimum, and maximum. All data collected, including unscheduled visits, will be presented in data listings. Summary tables will be limited to planned visits.

Subjects with missing data for a parameter will be excluded from the summary of this parameter.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC) Version 9.3 or above in Unix (Sun OS) environment.

3.2 Subject Populations

The following subject populations will be used when summarizing the data:

- **Evaluable population for DLT:** includes all subjects in the dose -escalation phase who receive at least 1 full cycle of MEDI-551 and complete safety follow-up through the DLT evaluation period (defined in Section 4.5.6 of the protocol) or experience any DLT. The evaluable population for DLT will be used for the MTD analysis.
- **Safety population:** includes all subjects who receive any treatment of MEDI-551. It will be used to evaluate baseline characteristics as well as all endpoints for the safety.
- **Evaluable population for efficacy**: includes all subjects who receive any treatment of MEDI-551 and complete at least one post-baseline disease assessment. It will be used to evaluate the efficacy endpoints.

The number and percent of subjects in each subject population for evaluation will be summarized by dose level and overall (all subjects combined). The number of screen failures will be also summarized.

3.3 Subject Disposition

The following summaries will be prepared for subject disposition by dose level and overall.

Summary	Population
Number of Subjects Enrolled by Site	All subjects enrolled
Subject Status at the End of Study Therapy	Safety
Subject Status at the End of Study and Mortality Summary	Safety

The number and percentage of subjects enrolled and the study duration will be summarized by site number, the primary investigator's name, and location. The total number of subjects enrolled will be used as the denominator.

The summary of subject status at the end of study therapy will include the number and percentage of subjects who discontinued treatment due to completion of protocol-defined end of treatment (up to 2 more cycles of MEDI-551 after complete response), adverse event, death, lost to follow-up, withdrawal of consent, physician decision, non-compliance with investigational product, pregnancy, progressive disease, protocol violation, technical problems, other. The denominator for these summaries will include all subjects in the safety population.

Subject status at the end of study and mortality summary includes the number and percentage of subjects who ended the study due to completion of protocol-defined end of study, lost to follow-up, withdrawal of consent, death, or other. For the subjects who withdrew from the study, the reason for withdrawal (adverse event [AE] or other) will be summarized. For the subjects who are dead at the end of the study, the cause of death (due to disease, not due to disease) and the relationship of death to investigational product (none, remote, possible, probable, definite) will be summarized. For those subjects who died, the cause of death (due to disease, not due to disease) and the relationship of death to investigational product (none, remote, possible, probable, definite) will also be summarized. The denominator for these summaries will include all subjects in the safety population.

3.4 Baseline Characteristics

Summaries on demographics, disease history, prior cancer treatment, baseline disease status, baseline bone marrow and aspirate assessment, Karnofsky performance status and other baseline disease characteristics will be provided by dose level and overall to describe the subject population in this study. They will aid in interpretation of the assessment of the primary and secondary objectives and provide an overview of study conduct. The following parameters will be summarized for the safety population:

Summary	Population
Demographics	Safety
Disease History	Safety
Prior Cancer Treatment	Safety
Baseline Disease Status Assessment	Safety
Baseline Bone Marrow Biopsy and Aspirate Assessment	Safety
Baseline SPEP and UPEP Assessment	Safety
Baseline Spleen and Liver Assessment	Safety
Baseline Karnofsky Performance Status	Safety

Demographics will be summarized for the continuous variables: age (years), height (cm) and weight (kg) using descriptive statistics. Frequency distributions will be provided for the categorical variables: gender, race and ethnicity.

Disease history summary will include descriptive statistics for time from the initial diagnosis to study entry and frequency distributions for the stage of initial diagnosis (I, II, III, IV), constitutional symptoms at diagnosis (absent, present) and type of transplant (hematopoietic stem cell, bone marrow, none) for all subjects as well as by disease type (CLL, DLBCL, FL, MM, MCL).

Baseline disease status assessment summary will include frequency distributions for the current stage (I, II, III, IV), constitutional symptoms (absent, present), any spleen involvement, any liver involvement and other organ involvement for all subjects as well as by disease type (CLL, DLBCL, FL, MM, MCL).

The summary of prior cancer treatment will include the number and percent of subjects who had received prior therapies in the following categories: biologic, chemotherapy, radiation, surgery, hormonal and other for all subjects and by disease type. The best response to the last cancer treatment will be also summarized by disease type.

Baseline bone marrow biopsy and aspirate assessment will include frequency distributions of subjects who have received bone marrow biopsy and aspirate, presence of malignant cells for DLBCL, MCL and FL subjects, presence of lymphocytes and nodules for CLL subjects, and presence of plasma cells for MM subjects.

For the baseline SPEP and UPEP assessment the results of these two tests will be presented in a listing.

The baseline spleen and liver assessment summary will include the number and percent of subjects with liver enlarged (by palpation) and spleen enlarged (by palpation) presented for all subjects as well as by disease type.

Karnofsky performance status will be summarized using frequency distribution for the categories: <70, 70, 80, 90, and 100 for all subjects.

3.5 Study Drug Exposure

The following summary of study drug exposure will be provided for the safety population by dose level and overall as well as by disease type (CLL, DLBCL, FL, MM, MCL). In

addition, summaries for study treatment change and subsequent alternative cancer treatment will be provided for the safety population by dose level and overall.

Summary	Population
Study Treatment Exposure	Safety
Summary of Study Treatment Change	Safety
Summary of Subsequent Alternative Cancer Treatment	Safety

Summary of study treatment exposure includes descriptive statistics for the number of doses received during the study, total dose received, and total number of treatment cycles, defined as the number of cycles during which subject received at least one dose of MEDI-551. The total number of treatment cycles of MEDI-551 will also be summarized using frequency distribution for categories to be defined in the Statistical Programming Plan (SPP). The dose intensity of the study treatment is a percent of total actual dose that a subject received during the study treatment period versus total intended dose for the same study treatment period according to the study protocol. It will be summarized using descriptive statistics as part of study treatment exposure summary. The formula provided below gives calculation details for the dose intensity:

$$\text{Dose Intensity } (\%) = 100 \times \frac{\sum \text{dose received } (mg/kg)}{\text{intended dose } (mg/kg) \times \text{treatment period}}$$

where

$$\text{Dose received } (mg/kg) = \text{dose level}(mg/kg) \times \frac{\text{Actual volume } (mL)}{250\ mL}$$

The summary of study treatment change will present the total number of subjects with dose delay, the reasons for dose delay (adverse events, scheduling conflict, other), the total number of subjects for whom the entire dose was not administered as scheduled, the reasons entire dose was not administered as scheduled (adverse events, other) and the reason subject did not receive investigational product (adverse events, other) will be summarized using frequency distribution.

The use of subsequent alternative cancer treatment after the discontinuation of study drug will be summarized by type of treatment using frequency distribution.

3.6 MTD or OBD/Highest Protocol-Defined Dose

The MTD will be based on the evaluable population for DLT and will be defined as the highest dose at which ≤ 1 out of 6 subjects experience a DLT during the DLT evaluation period. The number and percentage of subjects with a DLT will be presented by dose level and overall. If the MTD is not reached, the OBD (Arm A) or highest protocol-defined dose (Arms B and C) will be determined based upon analysis of all available data, including safety, PK, pharmacodynamics, and response.

3.7 Safety Assessments

Safety endpoints will be summarized descriptively. The occurrence of AEs, abnormal laboratory values, and SAEs reported will be summarized for all subjects who received any MEDI-551. Adverse events and SAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE V4.03) and described by system organ class and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to MEDI-551. Frequency rates will be calculated for each system organ class and MedDRA preferred term. All summaries will be done by dose level and overall and will be based on the safety population.

The toxicity profile will be assessed primarily by summarizing adverse events, serious adverse events, significant or important clinical findings in electrocardiogram (ECG) results, Karnofsky performance status (summarized by worst performance status during the study) and laboratory assessments during the study. All summaries for toxicity profile evaluation will be done by dose level and overall, and will be based on the safety population.

Adverse Events and Serious Adverse Events

Treatment-emergent adverse events (TEAEs), defined as events present at baseline that worsen in intensity after administration of study drug, or events absent at baseline that emerge after administration of study drug, will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, severity graded according to NCI CTCAE V4.03 (grade 1, grade 2, grade 3, grade 4, grade 5), and relationship to study drug.

Subjects will be counted only once for each preferred term, once for each system organ class, and by the highest event severity, regardless of how many events the subject experienced. The following treatment emergent adverse event summaries will be provided:

Summary	Population
Rate Summary of All Treatment Emergent Adverse Events	Safety
Number of Subjects with Treatment Emergent Adverse Events	Safety
Number of Subjects with Treatment Emergent Adverse Events by Highest Severity	Safety
Number of Subjects with Treatment Emergent Adverse Events Sorted by Frequency	Safety
Number of Subjects with Related Treatment Emergent Adverse Events	Safety
Number of Subjects with Related Treatment Emergent Adverse Events by Highest Severity	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events by Serious Adverse Event Criteria	Safety
Number of Subjects with Related Treatment Emergent Serious Adverse Events	Safety
Number of Subjects with Treatment Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug	Safety

The AEs/SAEs occurring from the signing of the informed consent and prior to the initiation of study treatment will be listed. The AEs/SAEs that begin 30 days after last dose will not be summarized or listed.

Laboratory Parameters

The change in each laboratory parameter from baseline to the "worst-case" (nadir and/or zenith) and to the last assessment for hematology/coagulation and blood chemistry will be summarized by descriptive statistics (N, mean, standard deviation, median, minimum, maximum). Baseline values will be defined as the last valid assessment prior to the first dose of MEDI-551.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE V4.03 will be derived according to laboratory values. Laboratory abnormalities will be presented. Shift tables from baseline to the maximum severity grade and to the last assessment will be generated for each of laboratory parameter.

The following summaries for lab parameters will be prepared.

Summary	Population
Change from Baseline in Hematology/Coagulation Parameters	Safety
Change from Baseline in Chemistry Parameters	Safety
Toxicity Grades for Hematology/Coagulation Parameters	Safety
Toxicity Grades for Chemistry Parameters	Safety

Results of urine protein electrophoresis, serum protein electrophoresis, urinalysis, cytogenetic analysis, and flow cytometry will be listed by subject and visit.

ECG Parameters and Karnofsky Performance Status

The following summaries will be provided for ECG parameters and Karnofsky performance status:

Summary	Population
Change from Baseline in ECG parameters	Safety
Summary of ECG clinical findings	Safety
Summary of Karnofsky performance status	Safety

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, QTcB [Bazett], QTcF [Fridericia]), including change from baseline, will be provided for each scheduled time point. ECG clinical findings will be summarized at each time point in terms of overall ECG interpretation (within normal limits, abnormal insignificant, abnormal significant, un-interpretable and incomplete analysis) as well as comparison with baseline interpretation (improved, worsened, unchanged, not compared).

Karnofsky performance status will be summarized using a shift table from baseline to the worst performance status and to the last assessment.

Vital Signs

Descriptive statistics of value and change from baseline value for heart rate, blood pressure, temperature, weight and respiratory rate will be provided for each scheduled time point. The following summary will be prepared for vital sign parameters based on the safety population.

Summary	Population
Change from Baseline in Vital Sign Parameters	Safety

3.8 Efficacy Assessments

The efficacy will be assessed based on CR, duration of CR, objective response, disease control, TTR, duration of objective response, duration of disease control, PFS, and OS.

Anti-tumor Activity of Medi-551

To evaluate the anti-tumor activity of MEDI-551, summaries for CR rate, duration of CR, best disease response, objective response rate, disease benefit rate, time to response, duration of objective response, time to progression, progression free survival and overall survival will be performed by dose level and overall (all doses combined) based on the evaluable

population for efficacy for each of the advanced B-cell malignancies CLL, DLBCL, FL and MM. These summaries will be repeated using the per-protocol population.

Complete Response Rate

The CR rate is defined as the proportion of subjects that have achieved CR in the safety population. The 95% and 80% confidence interval (CI) of the CR rate will be estimated based on the exact probability method (Clopper-Pearson exact interval). As a supportive analysis, the CR rate and its 95% and 80% CI will be estimated based on the evaluable population for efficacy.

Duration of Complete Response

Duration of CR will be measured from the first documentation of a CR to the time of progressive disease/relapse. Duration of CR will be censored on the date of last disease assessment for subjects who have no documented relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of CR will be calculated using the Kaplan-Meier method for the subgroup of subjects with CR. Also, as a supportive analysis, the duration of CR will be evaluated based on the evaluable population for efficacy.

MRD-negative CR

Subjects with CR and negative MRD defined as the proportion of subjects with a best response of CR and without MRD. The MRD rate is defined as the proportion of subjects that have achieved CR in the safety population. The 95% and 80% confidence interval (CI) of the CR rate will be estimated based on the exact probability method (Clopper-Pearson exact interval).

Best Disease Response

The best overall response during the study will be calculated and summarized with number and percentage of subjects for the following categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Objective Response Rate

Objective response rate is defined as the proportion of subjects with CR or PR. The denominator of ORR in the summary for the safety population will be equal to the number of subjects in this population. Subjects that have missing overall response assessments will be considered non-responders, so they will be counted in the denominator, but not in the

numerator of ORR. The 95% CIs of ORR will be estimated using the exact probability method (Clopper-Pearson exact interval).

Disease Control

Disease control includes CR, PR, or SD for at least 8 weeks.

Time to Response

Time to response (TTR) is measured from the start of MEDI-551 treatment to the first documentation of disease response (CR or PR) and will be evaluated only in subjects who receive any treatment of MEDI-551 and have achieved objective response (CR or PR). TTR is calculated in months as follows:

TTR (months) = (Date of first disease response – Date of MEDI-551 start + 1) / (365.25/12)

TTR will be summarized using Kaplan-Meier estimates (median time, 95% CI for median time).

Duration of Objective Response

Duration of objective response (DOR) is measured from the first documentation of objective response to the first documented progressive disease (PD) or relapse. DOR is calculated in months as follows:

DOR (months) = (Date of PD/relapse or censoring – Date of first response + 1) / (365.25/12),

where date of PD/relapse or censoring is given in Table 3.8-1. DOR will be summarized using Kaplan-Meier estimates (median time, 95% CI for median time).

Table 3.8-1 Definition and censoring information for DOR

Situation	Date of PD/relapse or Censoring	Outcome
PD or relapse	Date of earliest sign of PD or relapse	Progressed
No PD or relapse	Date of last disease assessment	Censored
PD or relapse after ≥ 2 missed consecutive disease assessments	Date of last disease assessment	Censored

Duration of Disease Control

Duration of disease control will be defined as the time period from start of MEDI-551 administration to the event of PD/relapse. Duration of disease control will be censored on the date of last disease assessment for subjects who have no documented PD/relapse prior to data cutoff, dropout, or the initiation of alternative anticancer therapy. Duration of disease control will only be calculated for the subgroup of subjects with best response of CR, PR, or SD, and will be evaluated using the Kaplan-Meier method.

Time to disease progression/relapse

Time to disease progression/relapse (TTP) is measured from the start of MEDI-551 treatment until the first documentation of disease progression or relapse. TTP is calculated in months as follows:

TTP (months) = (Date of PD/relapse or censoring – Date of MEDI-551 start + 1) / (365.25/12),

where date of PD/relapse or censoring is given in Table 3.8-2. TTP will be summarized using Kaplan-Meier estimates (median time, 95% CI for median time).

Table 3.8-2 Definition and censoring information for TTP

Situation	Date of PD or Censoring	Outcome
PD or relapse	Date of earliest sign of PD or relapse	Progressed
No PD or relapse	Date of last disease assessment	Censored
PD or relapse after ≥ 2 missed consecutive disease assessments	Date of last disease assessment	Censored
No disease assessment at baseline or post-baseline visits	Date of first MEDI-551	Censored

Progression-free survival

Progression-free survival (PFS) is measured from the start of MEDI-551 treatment until the first documentation of disease progression, relapse or death, whichever occurs first. PFS is calculated in months as follows:

PFS (months) = (Date of PD/relapse/death or censoring – Date of MEDI-551 start + 1) / (365.25/12),

where date of PD/relapse/death or censoring is given in Table 3.8-3. PFS will be summarized using Kaplan-Meier estimates (median time, 95% CI for median time).

Table 3.8-3 Definition and censoring information for PFS

Situation	Date of PD/relapse/death or Censoring	Outcome
PD or relapse	Date of earliest sign of PD or relapse	Progressed
Death before the first post-baseline disease assessment or after disease assessments documenting no PD	Date of death	Death
No PD, death or relapse	Date of last disease assessment	Censored
PD/relapse/death after ≥ 2 missed consecutive disease assessments	Date of last disease assessment	Censored
No disease assessment at baseline or post-baseline visits	Date of first MEDI-551	Censored

Overall survival

Overall survival (OS) is measured from the start of MEDI-551 treatment until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects were known to be alive. OS is calculated in months as follows:

OS (months) = (Date of death or censoring – Date of MEDI-551 start + 1) / (365.25/12).

OS will be summarized using Kaplan-Meier estimates (median time, 95% CI for median time).

3.9 Pharmacokinetic Assessments

To support the pharmacokinetic assessments of MEDI-551, analysis of pharmacokinetic parameters of MEDI-551 will be performed and reported by the MedImmune Global PK-PD & Bioanalysis group. The PK of MEDI-551 will be estimated by non-compartmental analysis. A population PK analysis may also be performed to obtain additional PK parameters. Those PK parameters will be summarized by descriptive statistics including N, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean.

3.10 Assessment of Effect on Circulating Lymphocyte Populations

Circulating levels of blood mononuclear cells, including T-cells, B-cells, NK cells and monocytes will be determined using standard clinically available flow cytometry. B-cell levels will be monitored from start of treatment until recovery.

Recovery will be defined as a B-cell count of ≥ 200 cells/mm^3 in subjects with baseline B-cells of ≥ 200 cells/ mm^3 or two consecutive B-cell counts within ± 20% of baseline or above in subjects with baseline B-cell counts of < 200 cells/ mm^3. It will be defined only for the

subjects with a nadir level of < 200 cells/mm^3 and baseline B-cell level greater than the nadir level. It will be summarized by presenting the number and percentage of subjects with B-cell recovery by dose level and overall.

Time to B-cell recovery will be defined for the subjects with B-cell recovery as

- the time from nadir to first B-cell level ≥ 200 cells/mm^3 for the subjects with baseline B-cell levels ≥ 200 cells/mm^3 or
- the time from nadir to the first of the 2 consecutive values within ± 20% of baseline or above, if such 2 consecutive values are observed, for the subjects with baseline B-cell < 200 cells/mm^3.

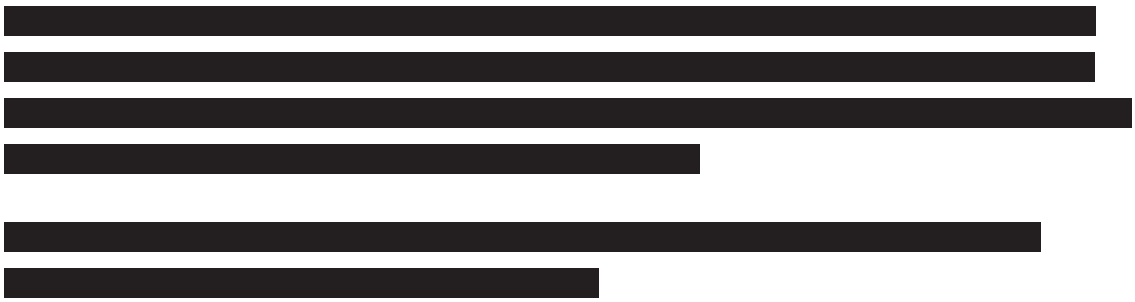
Time to recovery will be summarized in subjects with recovery using descriptive statistics.

Quantitative immunoglobulin (IgM, IgG, IgA, IgE) levels will be summarized using descriptive statistics for each scheduled time-point during treatment and at the time of B-cell recovery, if sufficient immunoglobulin level data are collected at this time. A plot of the immunoglobulin levels and B-cell actual values or descriptive statistics, if sufficient data is available, across time will be done considering all the time point at which both immunoglobulin and B-cell levels are collected. All summaries will be done for the safety population.

3.11 Immunogenecity Assessments

The immunogenic potential of MEDI-551 will be assessed by summarizing the presence of anti-MEDI-551 antibodies with number and percentage of subjects in each category: present, absent for each scheduled time point. In addition, the number of treatment cycles prior to developing anti-MEDI-551 antibodies will be summarized using descriptive statistics. All summaries will be done for the safety population.

3.12 Exploratory Summaries



4 INTERIM SAFETY ANALYSES

An interim safety analysis will be undertaken when the MTD or OBD has been established, and prior to enrollment in the expansion phase. Treatment emergent AEs, SAEs, laboratory assessments and concomitant medications at subject level will be provided to evaluate the safety of MEDI-551.

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