MedImmune

MEMORANDUM

DATE: July 25, 2017
TO: Study File
FROM: [redacted]
RE: CD-ON-CAT-8015-1053 Statistical Analysis Plan Approval

The Statistical Analysis Plan (version 5) for Protocol CD-ON-CAT-8015-1053 has been reviewed and approved.

[redacted]

Statistical Analysis Plan

A Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell Leukemia

Protocol Number: CD-ON-CAT-8015-1053

NCT #: NCT01829711

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LIST OF IN-TEXT TABLES

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	antidrug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BICR	blinded independent central review
BOR	best overall response
CBC	complete blood count
CFR	code of federal regulations
CI	confidence interval
CLS	capillary leak syndrome
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
ECG	electrocardiogram
EOT	end of treatment
GCP	good clinical practice
HCL	hairy cell leukemia
H/E	hematoxylin and eosin
HGB	hemoglobin
HUS	hemolytic uremic syndrome
HR	hematologic remission
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IRB	Institutional Review Board
ITT	intention-to-treat
IV	intravenous
MedDRA	Medical Dictionary For Regulatory Activities
MRD	minimal residual disease
NAb	neutralizing antibodies
NE	non-evaluable
OR	objective response
ORR	overall response rate
PD	progressive disease/ pharmacodynamics
PFS	progression-free survival

Abbreviation or Specialized Term	Definition
PK	pharmacokinetics
PLT	platelet
PNA	purine nucleoside analog
PR	partial response
PT	preferred term
QTc	corrected QT interval
QTcB	QTc corrected by Bazett's formulas
QTcF	QTc corrected by Fridericia's formulas
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SPP	statistical programming plan
TTF	time to treatment failure
TTR	time to response
ULN	upper limit normal

1 INTRODUCTION

This document describes the statistical analysis methodology and summaries for protocol CD-ON-CAT-8015-1053 [redacted] a pivotal multicenter, single-arm study of moxetumomab pasudotox in subjects with relapsed or refractory hairy cell leukemia (HCL). 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 are planned to be created in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1.1 Study Objectives

2.1.2 Primary Study Objective

The primary objective of this study is to determine the rate of durable complete response (CR) in multiple relapsed HCL with moxetumomab pasudotox. To meet the primary endpoint, subjects will need to meet standard criteria for CR by analysis of blood, bone marrow and imaging, and maintain a hematologic remission (HR), namely the blood counts needed for CR, for >180 days.

2.1.3 Secondary Study Objectives

The secondary objectives are to:

- Determine the overall response rate (ORR), progression-free survival (PFS), Time to treatment failure (TTF), and duration of responses (CR and partial response [PR]).
- Confirm the tolerability and safety of moxetumomab pasudotox in subjects with HCL.
- Evaluate immunogenicity and pharmacokinetics (PK) of moxetumomab pasudotox.

2.1.4 Exploratory Study Objectives

Not applicable.

2.2 Study Design

This is a pivotal multicenter, single-arm study of moxetumomab pasudotox in subjects with relapsed or refractory HCL. Subjects are eligible if they have histologically confirmed, immunotoxin-naive HCL or HCL variant with a need for therapy based on protocol-defined criteria, and have had at least 2 prior systemic therapies, including at least 2 prior courses of

a purine nucleoside analog (PNA), or 1 course of either rituximab or BRAF inhibitor following a single prior course of PNA.

Seventy-seven subjects will be enrolled to receive 40 µg/kg moxetumomab pasudotox administered by intravenous (IV) infusion over 30 minutes on Days 1, 3 and 5 of each 28 day cycle until the maximum duration of 6 cycles is completed, the subject progresses, unacceptable toxicity occurs, the subject begins alternate therapy, or documented CR (for subjects who have no assessable minimal residual disease). If ≤ 2 of the first 25 subjects do not achieve durable CR, no additional subjects will be accrued.

2.3 Treatment Assignment and Blinding

The study is not blinded. Each subject who meets the eligibility criteria will be assigned open-label moxetumomab pasudotox.

2.4 Sample Size

The sample size estimation in this study is based on the assumption that the historical durable CR rate in this population is ≤ 13%. This is based on previous studies of rituximab (Protocol Section 2.3.)

[redacted] Using the exact binomial test, a total of 77 subjects will provide 90% power to detect a difference between 28% and 13% durable CR rates at a 2-sided significance level of 0.05 [redacted]

3 STATISTICAL METHODS

3.1 General Considerations

Categorical data will be summarized by frequency distribution (number and percentage of subjects falling within each category). Continuous variables will be summarized by descriptive statistics including the number of subjects (N), mean, standard deviation, median, and range (minimum and maximum). Standard deviations will be presented with one more decimal point than the mean. In general, all calculations will be performed prior to rounding.

In general, subjects with missing data for a continuous parameter will be excluded from the summary of this parameter; subjects with missing data for a baseline discrete parameter will be grouped in the missing category; missing data for efficacy endpoints will not be imputed.

Tables will be supported by data listings showing the original data forming the basis for the summaries. All data will be provided in data listings sorted by subject number.

In general, unless stated otherwise, baseline will be defined as the last value prior to initial dosing.

All statistical tests will be two-sided at an alpha = 0.05 significance level unless stated otherwise. Two-sided confidence intervals, whenever specified, will be produced at 95%.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC) in a UNIX platform. The analytical results generated from all SAS® programs will be validated according to MedImmune SAS® programming standards and MedImmune validation procedures.

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	Subjects who have been entered into the study and treated by moxetumomab pasudotox.
Safety population	Subjects who received at least 1 dose of moxetumomab pasudotox.
Efficacy evaluable subject population	Subjects who received at least 1 dose of moxetumomab pasudotox, have a baseline with at least one indication for treatment (neutropenia [ANC <1000 cells/µL], anemia [hemoglobin <10g/dL], thrombocytopenia [platelets <100,000/µL], or symptomatic splenomegaly), have one baseline bone marrow biopsy and/or aspirate and cross sectional imaging and at least one post baseline disease assessment including both bone marrow examination and cross sectional imaging, or have died within 30 days after last dose.
PK population	All subjects who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

Subject disposition and completion status will be summarized for the ITT population. A summary of subjects screened and screen failures, reasons for screen failures, and subjects entered into and treated in the study will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and follow-up will be provided. Summaries of the number and percentage of subjects entered at each site will also be provided.

3.3.2 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the ITT population. Demographic information related to gender, age, race, weight, height and region will be presented. A summary of baseline disease characteristics may include, but will not be limited to duration from the initial diagnosis, spleen and liver size, bone marrow aspirate and/or biopsy assessment, lymph node size and HCL histology (classic or variant). Summaries of prior cancer therapy will include but will not be limited to minimum, maximum, median number of therapies, number and percentage of subjects with 2, 3, etc. prior therapies, number and percentage with prior PNA treatment courses and other therapy classes , best response achieved with the most recent regimen and refractory rate to prior PNA treatment courses.

3.3.3 Study Drug Exposure

Exposure will be summarized for the safety population. The number of treatment courses (cycles/doses), and total dose of study drug received per subject will be summarized. Number of doses is defined as the total number of doses received. Number of cycles is defined as the number of cycles during which a subject received at least one dose of study drug. A dose will be counted if treatment is started even if the full dose is not received.

The number of subjects experiencing dose delays due to toxicity or other reasons and the number of dose delays per subject will be summarized.

Summaries of relative dose intensity will be produced. Relative dose intensity is defined as the total actual dose that a subject received divided by the total intended dose. The details of the dose intensity calculation will be provided in the SPP.

3.3.4 Concomitant Medications

The number and percentage of subjects who took at least 1 dose of medication other than investigational product during the study will be summarized by the Anatomical Therapeutic Chemical (ATC) class and preferred term (PT) on the Safety population. Within each level of summarization, a subject will be counted once if he/she takes one or more medications.

Concomitant medications include those medications:

- With a start date greater than or equal to the date of the first dose of study medication, or
- With a start date prior to the date of the first dose of study medication and a stop date either after the date of first dose of study medication or marked as "continuing".

Transfusions and growth factors will be reported in a listing.

3.4 Protocol Deviations

Protocol deviation reports will be reviewed and the severity of each protocol deviation will be assigned by the study team. A complete list of important protocol deviations in the following categories can be found in the sponsor's Protocol Deviation Guidance Document.

- Inclusion and exclusion criteria
- Study drug
- Assessment – safety
- Lab/Endpoint data
- Visit window
- Informed consent
- Prohibited Co-Medication
- Overdose and/or Misuse
- Other

Incidence of important protocol deviations will be summarized by deviation categories. A listing will be provided with protocol deviation details. None of the deviations will lead to subjects being excluded from any analysis populations described in Section 3.2. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed.

3.5 Efficacy Endpoints and Analyses

Response criteria are based on previous HCL studies (Catovsky et al, 1987; Cheson et al, 1998; Grever et al, 1995; Hoffman et al, 1997). Although the requirements varied slightly among these trials, certain requirements are well accepted and considered standard. The response criteria are detailed in protocol Section 11.1.

3.5.1 Efficacy Endpoints

Primary endpoint is durable CR as derived from

- The overall response provided by BICR, and
- HR duration based on hematologic assessment: CBC, transfusions, growth factors information recorded on the case report form (CRF).

Secondary endpoints are CR, duration of CR, duration of HR, objective response (OR), time to objective response, duration of OR, PFS, and TTF.

3.5.1.1 Durable CR

Primary Analysis of Durable CR based on BICR

Durable CR is defined as the overall response that meets blood, bone marrow and imaging criteria for CR, followed by a >180 day duration of HR. HR is defined as meeting the following criteria:

- neutrophils ≥ 1.5 x 109/L with no neutrophils-related transfusions or growth factors in the previous 4 weeks,
- platelets ≥ 100 x 109/L with no platelets-related transfusions or growth factors in the previous 4 weeks, and
- hemoglobin ≥ 11.0 g/dL with no hemoglobin-related transfusions or growth factors in the previous 4 weeks.

If any of the blood counts among neutrophils, platelets and hemoglobin is missing, the rest of non-missing blood counts will be evaluated for HR. If any of the three criteria above is not met, HR will be considered as not achieved. Otherwise, HR will be considered as unknown.

A complete list of related transfusions and growth factors can be found in the Appendix. The list may be subject to change before the database lock.

Duration of HR from CR will be measured from the first documentation of CR (by imaging, bone marrow biopsy and blood counts) to the first time of loss of HR.

Data from the CRF on blood count (neutrophils, platelets and hemoglobin), transfusions, growth factors, and alternative anticancer therapies will be used to derive duration of HR.

Once a CR is achieved, the HR duration is not interrupted by transient decreases in normal blood counts. HR will be considered as lost if one or both of the following conditions are met:

- A blood count parameter does not meet the criterion for HR on ≥2 consecutive hematologic assessments (not followed by ≥2 additional consecutive hematologic assessments meeting the criterion for HR at a later time). Both consecutive sequences need to be ≥14 days in duration
- One hematologic assessment with abnormal blood count without any subsequent evaluable follow-up hematologic assessments

Duration of HR will be censored on the date of the last hematologic assessment for subjects who have no documented relapse based on blood count prior to data cutoff, dropout, or initiation of alternative anticancer therapy.

The rules to determine whether or not subjects have had an event (loss of HR) for duration of HR along with the date of event/censoring are specified in Table 3.5.1.1-1.

Table 3.5.1.1-1 Summary of Censoring Guidelines for Duration of HR

Situation	Date of Event or Censoring	Outcome
Loss of HR (without more than one consecutive missed or non-evaluable hematologic assessments or without initiation of alternative anticancer therapy)	Date of the first hematologic assessment with abnormal blood count	Event
HR prior to initiation of alternative anticancer therapy	Date of CR or last evaluable hematologic assessment demonstrating HR prior to initiation of alternative anticancer therapy, whichever occurred last	Censored
Loss of HR immediately after ≥ 2 consecutive missed or non-evaluable hematologic assessments	Date of CR or last evaluable hematologic assessment demonstrating HR prior to missed or non-evaluable hematologic assessments, whichever occurred last	Censored
HR (without alternative anticancer therapy)	Date of last evaluable hematologic assessment demonstrating HR	Censored

The time period for each hematologic assessment is defined as the protocol defined time between hematologic assessment + the protocol allowed visit window for this assessment. The time period to identify 2 consecutively missed hematologic assessments after documentation of CR that meets blood, bone marrow and imaging criteria per investigator or end of treatment assessment is defined as the sum of time periods of these 2 visits. A subject without hematologic assessments (due to missed visit or due to missing data on neutrophils, platelets or hemoglobin) within the time period defined in this way will be determined to have missed 2 consecutive hematologic assessments.

More specifically, for subjects with a disease assessment per investigator showing CR prior to or at the end of treatment assessment, the following time period will be used after the earliest date of the disease assessment per investigator showing CR:

- 74 days for the first 6 months
- 210 days for the 24 months thereafter
- 426 days thereafter.

For subjects without a disease assessment per investigator showing CR prior to and at the end of treatment assessment, the following time period will be used after the end of treatment disease assessment date per investigator:

- 210 days for the first 24 months
- 426 days thereafter.

Sensitivity Analysis of Durable CR based on BICR

Two sensitivity analyses will be performed to assess the impact of censoring rules on the robustness of the duration of HR estimate. The first sensitivity analysis will be performed to consider the event/censoring scenarios as specified in Table 3.5.1.1-2.

Table 3.5.1.1-2 Sensitivity Analysis 1: Summary of Censoring Guidelines for Duration of HR

Situation	Date of Event or Censoring	Outcome
HR prior to initiation of alternative anticancer therapy	One day after date of CR or one day after last evaluable hematologic assessment showing HR prior to initiation of alternative anticancer therapy, whichever occurred last	Event
Loss of HR (without more than one consecutive missed or non-evaluable hematologic assessments	Date of the first hematologic assessment with abnormal blood count	Event

Table 3.5.1.1-2 Sensitivity Analysis 1: Summary of Censoring Guidelines for Duration of HR

Situation	Date of Event or Censoring	Outcome
or without initiation of alternative anticancer therapy)		
HR (without more than one consecutive missed or non-evaluable hematologic assessments or without initiation of alternative anticancer therapy)	Date of last evaluable hematologic assessment showing HR	Censored
Loss of HR immediately after more than one consecutive missed or non-evaluable hematologic assessments	One day after date of CR or one day after last evaluable hematologic assessment showing HR prior to missed or non-evaluable hematologic assessments, whichever occurred last	Event
HR followed by more than one consecutive missed or non-evaluable hematologic assessments without additional follow up data prior to data cutoff	One day after date of CR or one day after last evaluable hematologic assessment showing HR prior to missed or non-evaluable hematologic assessments, whichever occurred last	Event
HR after more than one consecutive missed or non-evaluable hematologic assessments	Date of last evaluable hematologic assessment showing HR	Censored

The second sensitivity analysis will be performed by:

- Counting any relapse, disease progression or death as an event regardless of whether a patient initiates a subsequent anti-cancer therapy or has missed more than one hematologic assessment.
- Censoring patients at last evaluable assessment or hematologic assessment with documentation of CR or hematologic remission regardless of whether a patient initiates a subsequent anti-cancer therapy or has missed more than one hematologic assessment.

The event/censoring scenarios for the second sensitivity analysis are specified in Table 3.5.1.1-3.

Table 3.5.1.1-3 Sensitivity Analysis 2: Summary of Censoring Guidelines for Duration of HR

Situation	Date of Event or Censoring	Outcome
Loss of HR	Date of the first hematologic assessment with abnormal blood count regardless of whether a patient initiates any alternative anticancer therapy or has more than one consecutively missed or non-evaluable hematologic assessment	Event
HR	Date of CR or last evaluable hematologic assessment showing HR, whichever occurred last, regardless of whether a patient initiates any alternative anticancer therapy or has more than one consecutively missed or non-evaluable hematologic assessment	Censored

Durable CR based on the investigator assessment will be derived from the overall response assessed by investigator and HR based on the blood count data (neutrophils, platelets and hemoglobin) and transfusions/growth factors recorded on the CRF.

3.5.1.2 CR

CR is defined as best overall response (BOR) of CR.

BOR per BICR is defined as the best response (in the order of CR, PR, Stable disease [SD], Progressive disease [PD], Non-evaluable [NE]) among all overall responses recorded from the start of treatment until PD, relapse, or the last evaluable disease assessment in the absence of PD/relapse prior to initiation of alternative anticancer therapy or discontinuation of the study, whichever occurs first.

BOR per investigator assessment is based on both disease and clinical assessments prior to initiation of alternative anticancer therapy or discontinuation of the study, whichever occurs first.

3.5.1.3 Time to CR

Time to CR is defined as the time from the start of moxetumomab pasudotox administration to the first documentation of CR and will only be evaluated for subjects with a CR.

3.5.1.4 Duration of CR

Duration of CR is defined as the duration from documentation of CR to the time of relapse as defined in Section 11.1 of the protocol. Duration of CR per BICR will be censored on the date of the last disease assessment or hematologic assessment for subjects who are alive with no documented relapse prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. Duration of CR per investigator will be censored on the date of last disease assessment, clinical response assessment or hematologic assessment for subjects who are alive with no documented relapse prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. Duration of CR will only be evaluated for subjects with CR.

The rules to determine whether or not subjects have had an event for duration of CR along with the date of event/censoring are specified in Table 3.5.1.4-1 and Table 3.5.1.4-2.

Table 3.5.1.4-1 Summary of Censoring Guidelines for Duration of CR per BICR

Situation	Date of PD/Relapse/Death or Censoring	PFS Outcome
Relapse	Earliest date of a disease assessment showing a non-CR response after CR onset, earliest date of loss of HR after CR onset, or date of death, whichever is earlier	Event
No relapse or death at the time of analysis	Date of the last disease assessment or hematologic assessment	Censored
Relapse immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the last disease assessment or hematologic assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
Initiation of alternative anticancer therapy before relapse	Date of the last disease assessment or hematologic assessment prior to initiation of alternative anticancer therapy, whichever occurred last	Censored

Table 3.5.1.4-2 Summary of Censoring Guidelines for Duration of CR per Investigator

Situation	Date of PD/Relapse/Death or Censoring	PFS Outcome
Relapse	Earliest date of a disease assessment or clinical response assessment showing a non-CR response after CR onset, date of loss of HR, or date of death, whichever is earlier	Event
No relapse or death at the time of analysis	Date of the last disease assessment, clinical response assessment or hematologic assessment, whichever occurred last	Censored
Relapse immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the last disease assessment, clinical response assessment or hematologic assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
Initiation of alternative anticancer therapy before relapse	Date of the last disease assessment, clinical response assessment or hematologic assessment prior to initiation of alternative anticancer therapy, whichever occurred last	Censored

3.5.1.5 Objective Response

Objective response is defined as the BOR of CR or PR.

3.5.1.6 Time to Objective Response

Time to objective response is defined as the time from the start of moxetumomab pasudotox administration to the first documentation of response (CR or PR) and will only be evaluated for subjects with an OR.

3.5.1.7 Duration of Objective Response

Duration of objective response is defined as the time from the first documentation of objective response (CR or PR) to the date of relapse. Duration of objective response per BICR will be censored on the date of last disease assessment or hematologic assessment for subjects who have no documented relapse prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. Duration of objective response per investigator will be censored on the date of last disease assessment, clinical response assessment or hematologic assessment for subjects who have no documented relapse prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. Duration of objective response will follow similar censoring rules as duration of CR.

3.5.1.8 Progression Free Survival

Progression Free Survival (PFS) is defined as the time from the start of moxetumomab pasudotox administration to the date of the first of the following events:

- Relapse
- Progressive disease
- Death

PFS per BICR will be censored on the date of last disease assessment or hematologic assessment for subjects who are alive with no documented relapse or PD prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. PFS per investigator will be censored on the date of last disease assessment, clinical response assessment or hematologic assessment for subjects who are alive with no documented relapse or PD prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. The rules to determine whether or not subjects have had a PFS event along with the date of event/censoring are specified in Table 3.5.1.8-1 and Table 3.5.1.8-2.

Table 3.5.1.8-1 Summary of Censoring Guidelines for PFS per BICR

Situation	Date of PD/Relapse/Death or Censoring	PFS Outcome
Death, documented Progressive Disease (PD) or relapse	Earliest date of a disease assessment showing a PD/relapse, earliest date of hematologic relapse[a] or date of death, whichever is earlier	Event
Death prior to second scheduled post-baseline disease assessment without any post-baseline disease assessment or immediately after <=1 missed or non-evaluable disease assessment following an adequate post-baseline disease assessment	Date of death	Event
No PD/relapse or death at time of analysis or lost to follow-up	Date of last disease assessment or hematologic assessment, whichever occurred last	Censored
Death or PD/relapse immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the first dose of study treatment or last disease assessment or hematologic assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
Initiation of alternative anticancer therapy before PD/relapse or death	Date of last disease assessment or hematologic assessment prior to initiation of alternative anticancer therapy, whichever occurred last	Censored
No disease assessments or clinical response assessments or death after first dose of treatment	Date of the first dose of study treatment	Censored

[a] hematologic relapse is defined as meeting the relapse criteria from CBC as described in Section 11.1 of the protocol.

Table 3.5.1.8-2 Summary of Censoring Guidelines for PFS per Investigator

Situation	Date of PD/Relapse/Death or Censoring	PFS Outcome
Death, documented Progressive Disease (PD) or relapse	Earliest date of a disease assessment or clinical response assessment showing a PD/relapse, earliest date of hematologic relapse[a], or date of death, whichever is earlier	Event
Death prior to second scheduled post-baseline disease assessment without any post-baseline disease assessment or immediately after <=1 missed or non-evaluable disease assessment following an adequate post-baseline disease assessment	Date of death	Event
No PD/relapse or death at time of analysis or lost to follow-up	Date of last disease assessment, clinical response assessment or hematologic assessment, whichever occurred last	Censored

Table 3.5.1.8-2 Summary of Censoring Guidelines for PFS per Investigator

Situation	Date of PD/Relapse/Death or Censoring	PFS Outcome
Death or PD/relapse immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the first dose of study treatment or last disease assessment, clinical response assessment or hematologic assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
Initiation of alternative anticancer therapy before PD/relapse or death	Date of last disease assessment, clinical response assessment or hematologic assessment prior to initiation of alternative anticancer therapy, whichever occurred last	Censored
No disease assessments or clinical response assessments or death after first dose of treatment	Date of the first dose of study treatment	Censored

[a] hematologic relapse is defined as meeting the relapse criteria from CBC as described in Section 11.1 of the protocol.

3.5.1.9 Time to Treatment Failure

Time to treatment failure (TTF) is defined as the time from the start of moxetumomab pasudotox administration to the date of the first of relapse, PD, initiation of alternative anticancer therapy, or death due to disease or disease-related complication. TTF will be censored similar to PFS, but also censored for death not accompanied by relapse.

3.5.2 Efficacy Analyses

3.5.2.1 Analyses of Primary Efficacy Endpoint

Durable CR rate is defined as the proportion of subjects with durable CR. Durable CR rate based on the BICR and its 95% CI will be constructed using the exact probability method (Clopper-Pearson exact interval) in the ITT population. If the lower bound of the 95% CI is above 13% (or equivalently, the binomial exact test one-sided p-value <0.025), it will be concluded that the durable CR rate in this subject population is significantly higher than the historical control value of 13%.

Durable CR rate based on the investigator assessment and its 95% CI using exact probability method will be estimated in the ITT population as supportive analysis.

The analyses will also be performed in the efficacy evaluable population as supportive analysis.

[redacted]

3.5.2.2 Analyses of Secondary Efficacy Endpoints

Analyses of all secondary efficacy endpoints related to disease assessment will be performed based on BICR and investigator assessment data.

The analyses of secondary efficacy endpoints except for PFS and TTF will be performed in the ITT population and as supportive in the efficacy evaluable population. Analysis of PFS and TTF will be performed in the ITT population only.

CR, Time to CR, and Duration of CR

The CR rate is defined as the proportion of subjects that have achieved CR. The CR rate based on BICR and its 95% CI will be constructed using the exact probability method (Clopper-Pearson exact interval) in the ITT population. The proportion of subjects who have CR (MRD negative/positive from IHC) and its 95% CI using the exact probability method based on BICR will also be calculated in the ITT population. CR rate may be summarized by the same subgroups used for durable CR.

The number and percentage of all subjects categorized by their BICR BOR (CR [with MRD negative/positive by IHC], PR [with MRD negative/positive by IHC], SD, PD, and NE) will be presented in the ITT population. This table will also be produced based on the BOR from investigator's assessment using the MRD results from flow cytometry assessed at local study sites. Discrepancy between the BICR and the investigator assessment will be summarized.

Time to CR will be summarized by the Kaplan-Meier method for all subjects who achieve CR.

The median duration of CR and its 95% CI and landmark analysis of duration of CR (e.g., at 6 months, 18 months) will be estimated for the subgroup of subjects with CR using the Kaplan-Meier method. Estimates will also be displayed graphically as a Kaplan-Meier curve with the estimate of proportion still responding on the y-axis versus duration of CR in months on the x-axis.

For all subjects with a CR, the duration of CR will be displayed graphically as follows: individual subjects identified by subject number on the y-axis and a bar showing duration of response in months over the x-axis.

If data are available and there are a sufficient number of subjects, duration of CR will be summarized using the Kaplan-Meier method by MRD status. An additional plot will display duration of CR according to MRD status, i.e., separate Kaplan-Meier curves for CR with MRD and CR without MRD will be displayed on the same plot. Duration of CR may be summarized by the same subgroups used for durable CR.

Duration of HR from Onset of HR and Time to HR

The median duration of HR from onset of HR and its 95% CI and landmark analysis of duration of HR (e.g., at 6 months or 18 months) will be estimated, if feasible, for the subgroup of subjects with HR using the Kaplan-Meier method.

Similar analysis will be performed for duration of HR from onset of HR as sensitivity analysis for the subgroup of subjects with HR and CR.

Time to HR will be summarized by the Kaplan-Meier method for:

1. Subjects in the ITT population.
2. Subjects in the ITT population who achieved a CR.

OR, Time to Objective Response, and Duration of OR

ORR is defined as the proportion of subjects with a best response of CR or PR. The ORR and its 95% CI will be constructed using the exact probability method (Clopper-Pearson exact interval) in the ITT population based on BICR data. ORR may be summarized by the same subgroups used for durable CR.

Time to response will be summarized by Kaplan-Meier method for all subjects who achieve CR or PR.

The median duration of objective response and its 95% CI and landmark analysis of duration of CR (e.g., at 6 months or 18 months) will be estimated for the subgroup of subjects with OR using the Kaplan-Meier method. Kaplan-Meier curve will also be presented.

For all subjects with an objective response, the duration of response will be displayed graphically as follows: individual subjects identified by subject number on the y-axis and a bar showing duration of response in months over the x-axis. Censored response duration times will be indicated by a symbol at the end of the bar.

PFS and TTF

A Kaplan-Meier plot of PFS and estimate of median PFS and its 95% CI using the Kaplan-Meier method will be presented. The landmark 12-month PFS rate and 24-month PFS rate will be estimated based on the Kaplan-Meier curves along with their 2-sided 95% CIs.

A Kaplan-Meier plot of TTF and estimate of median TTF and its 95% CI using the Kaplan-Meier method will be presented.

3.5.2.3 Exploratory Efficacy Endpoints and Analyses

Not applicable.

3.6 Patient Reported Outcomes

Not applicable.

3.7 Pharmacodynamic Endpoint(s) and Analyses

Pharmacodynamic endpoints include lymphocyte subsets (Lymphocyte enumeration/TBNK) by flow cytometry and evidence of disease-associated B-cell clones using next-generation sequencing. The analyses of these endpoints are descriptive in nature. A change in lymphocyte subsets from baseline may be summarized.

More details of these analyses may be included in a separate document. Summaries and analyses for exploratory pharmacodynamic biomarkers may be reported outside the clinical study report in a separate report.

3.8 Other Additional Analyses

Not applicable.

3.9 Safety Analyses

Safety data including adverse events (AEs), serious adverse events (SAEs), laboratory parameters, electrocardiograms (ECGs), vital signs and Eastern Cooperative Oncology Group (ECOG) performance status, will be summarized in the safety population.

Unscheduled visit data will be included in all summary tables and plots for overview presentations that select a single observation per patient (e.g., minimum post-baseline value, maximum change from baseline). For summary tables and plots that are presented by visit, the post-baseline assessment (whether reported as a scheduled or unscheduled visit) closest to the scheduled visit date, calculated from the first day of dosing, will be used. The visit will be missing if no assessment was reported within the specified visit window around the scheduled date. If two assessments are equidistant from a scheduled visit, the earlier of the two will be used.

3.9.1 Adverse Events and Serious Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA 19.0) and assigned grades based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

A treatment-emergent adverse event (TEAE) is defined as any AE that occurs on or after the date of initial receipt of study treatment. Analysis of AEs (as described below) will be limited to TEAEs. Any AEs that are considered as non-treatment emergent will be presented in the listings only.

TEAEs observed through 30 days after the last dose of moxetumomab pasudotox will be used for reporting in all AE summary tables. Any AEs post 30 days after the last dose of study treatment will be presented in a separate summary.

AEs and SAEs will be summarized by system organ class (SOC) and preferred term according to severity and relationship to moxetumomab pasudotox. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported.

An overview summary of the number and percentage of subjects with at least 1 TEAE within the period defined above will be tabulated for each of the following categories:

- All TEAEs
- TEAEs with CTCAE grade 3 or higher
- TEAEs by Highest Severity
- TEAEs by frequency
- Treatment related TEAEs
- Treatment related TEAEs by frequency
- Treatment related TEAEs with CTCAE grade 3 or higher
- Treatment related TEAEs by Highest Severity
- Serious TEAEs
- Serious TEAEs by Highest Severity
- Serious TEAEs by Serious AE Criteria
- Treatment related Serious TEAEs
- TEAEs resulting in permanent discontinuation of moxetumomab pasudotox

- Treatment related TEAEs resulting in permanent discontinuation of moxetumomab pasudotox
- TEAEs resulting in dose delay/omit/interruption
- Treatment related TEAEs resulting in dose delay/omit/interruption
- TEAEs resulting in death

A summary of the most common adverse events (defined as those with an incidence of at least 5%) by preferred term will also be produced.

3.9.2 Adverse Events of Special Interest

AEs of special interest (AESIs) will be summarized using the same period as in Section 3.9.1.

Preferred terms used to identify AESIs will be listed before database lock. Grouped summary tables of certain MedDRA preferred terms will be produced. For each 'grouped' term, the number (%) of subjects experiencing any of the specified terms will be presented by the highest NCI CTCAE grade. Time to onset of first AE or CTCAE grade 3 or higher for each grouped term and preferred term within each group will also be produced, where appropriate.

Additional summaries of the above-mentioned grouped AE categories will include:

- Treatment emergent AESIs by outcome
- Treatment emergent AESIs by highest severity
- Related treatment emergent AESIs
- Treatment emergent AESIs resulting in permanent discontinuation of study drug
- Serious treatment emergent AESIs

Summary of total duration (days) for specific AEs of special interest may also be provided, where appropriate.

The number and frequency of subjects reporting hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), ocular events, or hepatic function abnormalities and the associated symptoms will be summarized.

The number of cycles/doses at the onset of HUS, CLS, or ocular events will be summarized if there are sufficient events. Change of immunogenicity and PK at the onset and resolution

of HUS, CLS, or ocular events from baseline will be summarized if there are sufficient events.

3.9.3 Deaths and Treatment Discontinuations due to Adverse Events

See Section 3.9.1.

3.9.4 Clinical Laboratory Evaluation

Laboratory parameters will be assessed at baseline as well as throughout the study. Blood chemistry, hematology, coagulation, and urinalysis will be listed for each subject and absolute value and change from baseline will be summarized by scheduled visits, "worst-case" (nadir and/or zenith) on treatment, and the last assessment on-treatment using descriptive statistics. On-treatment period is defined from the first administration of moxetumomab pasudotox through 30 days after the last dose of moxetumomab pasudotox.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived according to laboratory values. Shift tables from baseline to worst toxicity grade on treatment will be presented. Separate summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. In addition, the number and percentage of subjects experiencing at least 1-Grade shift, at least 2-Grade shift, and any shift to a worst post-baseline toxicity Grade of 3 to 4 from baseline will be summarized. For each lab test condition, percentages are calculated based on the number of treated subjects who have a baseline and at least one post-baseline assessment. In the shift table analysis, for a given subject, if a subject has both missing and non-missing CTCAE grades for one laboratory test, the missing CTCAE grade of that laboratory test will be treated as the lowest grade.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived for the following parameters:

Hematology: Anemia (Hemoglobin hypo), White Blood Cell, Neutrophils, Platelets, Lymphocytes

Serum chemistry: Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Alkaline Phosphatase (ALP), Total bilirubin, Creatinine (without taking baseline into account when deriving CTCAE grade), Albumin, Cholesterol, Magnesium hypo and hyper, Sodium hypo and hyper, Potassium hypo and hyper, Corrected calcium hypo and hyper, Glucose hypo and hyper, GGT, Lipase, Amylase

For selected parameters including thyroid function tests (TSH, and free T4) with no CTCAE grading shift tables from baseline to "worst-case" on treatment value will be provided. "Worst-case" on treatment value will be categorized as low (L), normal (N), or high (H) using laboratory reference range (on both directions).

Additional summaries will include a shift table for urinalysis (Bilirubin, Blood, Glucose, Ketones, Protein) comparing the baseline value to the maximum on-treatment value.

Liver Function Parameters

Subjects with elevated post-baseline ALT, AST or Total Bilirubin that fall into the following categories will be identified. Number and percentage of these subjects will be tabulated.

Liver Function Parameters	Category
ALT	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN • >10 × – <=20 × ULN • >20 × ULN
AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Total bilirubin	• >=2 × – <=3 × ULN • >3 × – <=5 × ULN • >5 × ULN
ALT or AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Potential Hy's law	• (AST >= 3 × ULN or ALT >= 3 × ULN) and concurrent total bilirubin >= 2×ULN[a]

ULN: upper limit of normal range.

[a] Total Bilirubin >= 2×ULN is defined as at least one case of post treatment TBL >= 2×ULN occurred within 8 days (+/- 8 days) of post treatment ALT >= 3×ULN or AST >= 3×ULN.

Individual subject data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" will be listed.

Laboratory values outside laboratory reference ranges will be identified in the listings.

3.9.5 Other Safety Evaluations

3.9.5.1 Vital Signs

Vital signs will be measured on study days noted in Protocol Section 10. Descriptive statistics will be provided for values of vital signs (including weight, temperature, heart rate, respiration rate, and blood pressure) and change from baseline at each scheduled time point, as well as for the maximum and minimum post-baseline values.

3.9.5.2 Electrocardiogram

ECG parameters will be listed by subject. Absolute values and changes from baseline to post-therapy in QTc will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum and number of subjects).

The number and percentage of subjects having the following notable ECG interval values on treatment will be summarized.

- QTcF and QTcB >450 msec, >480 msec and >500 msec
- Increase and decrease in QTcF and QTcB from baseline of >30 ms, >60 ms and of >90 ms

For the outlier analysis on the ECG intervals, only the subject with “new” cases (as compared to baseline) will be included for summary. “New” means the category of the QTc abnormality was not present at baseline and became present for at least one post-baseline ECG assessment. For example, a subject is classified as new QTc > 450 msec if that subject had a baseline QTc <=450 msec and had a maximum post-baseline QTc interval > 450 msec. Percentages are calculated based on the number of subjects who had a baseline and at least one post-baseline assessment.

3.9.5.3 ECOG

ECOG performance status will be summarized using a shift table showing change in ECOG from baseline to the worst performance status.

3.9.6 Subgroup Analyses

Not applicable.

3.10 Immunogenicity

Immunogenicity results will be listed for each subject and summarized for the safety population. Number and percentage of subjects in the following categories will be provided. Summary statistics of the maximum titer will be calculated for the ADA+/NAb+ categories.

- ADA positive at baseline and/or post-baseline visits
- Persistent positive, defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment
- Transient positive, defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥2 post-baseline assessments (with <16 weeks between first and last positive)
- Treatment-boosted, defined as baseline positive ADA titer that was boosted to a 4 fold or higher level following drug administration
- ADA positive subjects who are NAb positive at any visit (ADA+/NAb+)
- Specificity CD22 positive of ADA+/NAb+ at any visit
- Specificity PE38 positive of ADA+/NAb+ at any visit
- ADA+/NAb+ positive at baseline and post-baseline visits

Durable CR rate based on BICR and incidence of the following safety parameter will be calculated for the immunogenicity subgroups as described in Section 3.5.2.1 (provided there are ≥10 subjects in each group).

- HUS/HUS-like
- CLS
- Both HUS/HUS-like and CLS
- Increased creatinine
- Infusion-related reaction
- Severe hypersensitivity reactions to include anaphylaxis and serious allergic reactions
- Treatment related TEAE (Grade 3 and above)

The correlation analysis of ADA with exposure may be performed by the MedImmune Global PK-PD & Bioanalysisgroup or designee, and will be included in the Clinical Pharmacokinetics and ADA Interpretive Report.

3.11 Pharmacokinetics

Individual moxetumomab pasudotox serum concentrations will be tabulated by treatment cycles along with descriptive statistics. Noncompartmental PK data analysis will be performed for Cycle 1 and 2 concentration data using scheduled or actual PK sample collection times.

If data allows, descriptive statistics of noncompartmental PK parameters will be provided. Due to the limited sampling schedule, population PK data analysis will be performed to better characterize the PK parameters of moxetumomab pasudotox in this subject population. A separate analysis will be prepared by MedImmune Global PK-PD & Bioanalysis group or designee for the population analysis.

Pharmacokinetic data analyses will be performed by the MedImmune Global PK-PD & Bioanalysis group or designee.

5 REFERENCES

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APPENDIX

Table A. Statistical Analysis Plan Amendments

SAP Version	Date	Key Details of Amendment	Reason for Amendment
Version 2.0	11MAY2016	• Removed relapse-free survival as a secondary endpoint • [redacted] • Revised language in the AE and SAE section (Section 3.8.1) • Added AESI and the associated symptoms (Section 3.8.2) • Clarifications added to clinical laboratory evaluation (Section 3.8.4) • Clarifications added to ECG summaries (Section 3.8.5.2) • Revised language in the interim analysis section (Section 4)	• To follow the MedImmune SAP template • To be aligned with protocol language
Version 3.0	11NOV2016	• Added the protocol deviation summaries (Section 3.4) • Revised definition of PNA refractory (Section 3.5.2.1) • [redacted]	• To expand the scope of analyses based on communications with agency • To provide a more clinically meaningful definition of PNA refractory

SAP Version	Date	Key Details of Amendment	Reason for Amendment
		• Clarifications added to the immunogenicity analyses (Section 3,10) • Revised language in the interim analysis section (Section 4.2)	
Version 4.0	21APR2017	• Revised definition of loss of HR (Section 3.5.1.1) • Clarifications added for duration of CR derivation (Section 3.5.1.4) • Clarifications added for PFS (Section 3.5.1.8) • Clarifications added to analyses of secondary efficacy endpoints (Section 3.5.2.2) • [redacted]	• To update the algorithm of identifying transient abnormal lab values • To clarify the derivation of BICR and investigator assessed efficacy endpoints
Version 5.0		• Added sensitivity analyses related to duration of HR. • Clarifications added to the determination of 2 missed consecutive hematologic assessments. • Clarifications added to the definition of potential Hy's law.	• Updates based on the feedback from FDA

Table B. Related Transfusions and Growth Factors

Category: Blood Transfusion

ATC4 Code	ATC4 Description	Preferred Term	Related Hem Parameter
B05AX	Other blood products	BLOOD, WHOLE	HgB and Platelet
B05AX	Other blood products	BLOOD CELLS, PACKED HUMAN	HgB
B05AX	Other blood products	PLATELETS, HUMAN BLOOD	Platelet
B05AX	Other blood products	HUMAN RED BLOOD CELLS	HgB
B05AX	Other blood products	RED BLOOD CELLS	HgB
B05AX	Other blood products	RED BLOOD CELLS, CONCENTRATED	HgB

ATC4 Code	ATC4 Description	Preferred Term	Related Hem Parameter
B05AX	Other blood products	RED BLOOD CELLS, LEUCOCYTE DEPLETED	HgB
B05AX	Other blood products	LEUCOCYTES	Neutrophil

Category: Haematopoietic Growth Factor

ATC4 Code	ATC4 Description	Preferred Term	Verbatim Term	Related Hem Parameter
B03XA	Other antianemic preparations	ERYTHROPOIETIN		HgB
B03XA	Other antianemic preparations	ERYTHROPOIETIN HUMAN		HgB
B03XA	Other antianemic preparations	EPOETIN ALFA		HgB
B03XA	Other antianemic preparations	EPOETIN BETA		HgB
B03XA	Other antianemic preparations	EPOETIN DELTA		HgB
B03XA	Other antianemic preparations	DARBEPOETIN ALFA		HgB
B03XA	Other antianemic preparations	NOVEL ERYTHROPOIESIS STIMULATING PROTEIN		HgB
B03XA	Other antianemic preparations	EPOETIN NOS		HgB
B03XA	Other antianemic preparations	ALBUMIN NOS+DARBEPOETIN ALFA (ALBUMIN NOS,DARBEPOETIN ALFA)		HgB
B03XA	Other antianemic preparations	CERA		HgB
B03XA	Other antianemic preparations	PEGZEREPOETIM ALFA		HgB
B03XA	Other antianemic preparations	PEGINESATIDE		HgB
B03XA	Other antianemic preparations	EPOETIN THETA		HgB
L03AA	Colony stimulating factors	LEUCOGEN (FILGRASTIM)		Neutrophil
L03AA	Colony stimulating factors	GRANULOCYTE MACROPHAGE COLONY STIM FACTOR		Neutrophil
L03AA	Colony stimulating factors	SARGRAMOSTIM		Neutrophil
L03AA	Colony stimulating factors	MOLGRAMOSTIM		Neutrophil
L03AA	Colony stimulating factors	GRANULOCYTE COLONY STIMULATING FACTOR		Neutrophil

ATC4 Code	ATC4 Description	Preferred Term	Verbatim Term	Related Hem Parameter
L03AA	Colony stimulating factors	FILGRASTIM		Neutrophil
L03AA	Colony stimulating factors	LENOGRASTIM		Neutrophil
L03AA	Colony stimulating factors	ANCESTIM		Neutrophil
L03AA	Colony stimulating factors	PEGFILGRASTIM		Neutrophil
L03AA	Colony stimulating factors	MIRIMOSTIM		Neutrophil
L03AA	Colony stimulating factors	THROMBOPOIETIN		Platelet
B02BX	Other systemic hemostatics	ELTROMBOPAG		Platelet
B02B	VITAMIN K AND OTHER HEMOSTATICS	VITAMIN K AND OTHER HAEMOSTATICS ()	Romiplostim	Platelet