STATISTICAL ANALYSIS PLAN

A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B Cell Lymphoma (DLBCL)

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	02 OCT 2017	
Amendment 1 (v2.0)	**15 FEB 2021**	All text has been updated for conducting primary analysis based on the Protocol amendment 5 and the decision of not to proceed into part 2 phase of study.

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Table of Abbreviations

Abbreviation/Acronym	Definition
ADPC	Analysis Dataset for PK Concentrations
AE	Adverse Event
AMQs	Amgen MedDRA Queries
CDM	Clinical Data Management
CR	Complete **Response**
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-Cell Lymphoma
DLRT	Dose Level Review Team
DRT	**Data Review Team**
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRE	Disease Related Events
ECG	Electrocardiogram
ECI	Event of Clinical Interest
EOI	Events of interest
E-R analysis	Exposure Response Analysis
FAS	Full Analysis Set
GSO-DM	Global Study Operations-Data Management
HSCT	Hematopoietic Stem Cell Transplantation
IA	Interim Analysis
IP	Investigational Product
IPD	Important Protocol Deviations
IPI	International Prognostic Index
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NGS	next generation sequencing
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival

Abbreviation/Acronym	Definition
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Remission
SAP	Statistical Analysis Plan
SMQs	Standard MedDRA Queries
SSAP	Supplemental Statistical Analysis Plan
WHODRUG	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **5** for the phase 1b blinatumomab in combination with pembrolizumab study 20150290, dated **December 03, 2019**. The scope of this plan includes the primary analysis and the final analysis that is planned and will be executed by the Global Biostatistics Science department unless otherwise specified. Pharmacokinetic, pharmacodynamic, exposure-response and biomarker analyses will be performed by Clinical Pharmacology Modeling and Simulation (CPMS) or biomarker group.

2. Objectives

2.1 Primary

To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab in adult subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL).

2.2 Secondary

To evaluate the safety, efficacy, and pharmacokinetics (PK) of blinatumomab in combination with pembrolizumab in adult subjects with r/r DLBCL

2.3 Exploratory

- To evaluate blood and tissue biomarkers
- To evaluate minimal residual disease (MRD) response by next generation sequencing (NGS)

3. Study Overview

3.1 Study Design

This is an open label, multicenter, phase 1b study testing the combination of blinatumomab with pembrolizumab in r/r DLBCL.

The study will consist of 2 portions:

- Part 1 (n = 6 – **30**) will test the safety of up to 3 different blinatumomab target dose levels in combination with pembrolizumab in a rolling 6 design. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and dose limiting toxicities (DLTs). Subjects who are not on the dose ultimately selected for part 2 will remain on their initial dose throughout the study.
- Part 2 (n = **40**) will consist of an expansion cohort to assess PK, safety, and preliminary efficacy data at the chosen target dose. The part 2 dose will be determined by the totality of the clinical data from part 1 as determined by the DLRT.

The study design includes:

- A 21-day screening period.
- A standard (core) treatment period of blinatumomab (first cycle) of 8 weeks
- A second (consolidation) cycle of blinatumomab of 28 days after a 28-day (± 3 days) blinatumomab treatment-free period that can be administered to subjects with stable disease (SD), partial **remission** (PR), or complete **remission** (CR).
- Pembrolizumab treatment until disease progression **or relapse** or up to 35 cycles in the absence of disease progression **or relapse**:
  - **To begin o**n study day 15 for subjects in cohort Ia

  OR

  - **To begin o**n study day 19 for subjects in cohort IIa and IIIa
- A safety follow-up visit after 30 days (+ 7 days) of last dose of each protocol specified therapy.

Follow-up for survival and collection of subsequent anticancer therapies will occur every 12 weeks (± 28 days) following blinatumomab safety follow-up visit for **until** approximately 24 months from the last dose of pembrolizumab.

Part 1 design and blinatumomab escalation/de-escalation rules

For part 1, subject enrollment will start in cohort Ia as outlined in the schema in Figure 1. Blinatumomab will be dosed as a continuous intravenous infusion (CIVI) for 8 weeks. The initial dose will be 9 μg/day and the dose will be escalated after 7 days to a target dose of 28 μg/day. Depending on tolerability, the target dose of blinatumomab will be increased to a maximum of **56** μg/day in cohort IIa **or** to **112** μg/day in cohort IIIa. Pembrolizumab will be dosed by intravenous (IV) infusion 200 mg at Q3W starting on study day 15 in cohort Ia, and on study day 19 in cohorts IIa and IIIa. Trial treatment of pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Subjects who do not meet the criteria for investigational product (IP) discontinuation (see below) are eligible for a second cycle of blinatumomab (consolidation) consisting of a CIVI of 28 days after a 28-day (± 3 days) blinatumomab treatment-free interval. Blinatumomab will be started at 9 μg/day and escalated every 7 days to the maximum target dose of blinatumomab in the assigned cohort.

Subjects will be enrolled to part 1 with up to 6 subjects being enrolled per cohort. In any cohort, tolerability **will be defined as** ≤ 1 DLT **out of 6 subjects**). **Expansion** to 10 subjects **will be allowed in any cohort** to ensure adequate safety and PK data is

collected. The decision to expand a cohort will be made by the DLRT. **In case of 10 subjects enrolled, tolerability is defined as ≤ 2 DLTs out of 10 subjects.**

The MTD of blinatumomab will be defined as the **highest** dose level at which at most 1 of 6 subjects **or at most 2 subjects in 10** experiences a DLT. The MTD defines the stopping rules for the study. For further details on replacement of subjects is given in Section 3.4 of protocol. The DLT criteria are defined in the Appendix E of the protocol.

The DLRT will meet to review the safety data when any of the following criteria are met:

- In two or more subjects **out of 6, a DLT has been reported, or 3 or more subjects out of 10, a DLT** has been reported in a cohort.
- Six subjects are enrolled in a cohort and all subjects have completed the DLT observation period.
- In the event that a cohort is expanded to 10, DLRT **will** also meet after all subjects have completed DLT observation period.

The DLRT will review the available data in part 1 to determine if the combination of blinatumomab and pembrolizumab is safe and tolerable as defined by DLT criteria. Based on the totality of the data, the DLRT may recommend **MTD, to escalate to the next dose level, or** to expand a cohort to a maximum of 10 subjects if the collection of more data is deemed warranted, **or to adjudicate DLT criteria (see Appendix E of protocol for details). At the end of Part 1, the cohort with recommended dose level requires to have at least 1** response out of 6 evaluable subjects or 2 responses out of 10 evaluable subjects **in order to proceed to Part 2.**

Part 2

For part 2, the dosing will be determined based on the safety of the combination of blinatumomab and pembrolizumab and the MTD of blinatumomab established in part 1 per DLRT. **For part 2, the DLT observation period will be determined by cohort chosen in Part 1 and Part 2 expansion.** Part 2 will consist of an expansion cohort to collect further safety and PK data as well as provide a preliminary estimate of the efficacy of the combination of blinatumomab and pembrolizumab. Dose limiting toxicities **and efficacy will be monitored by Data Review Team (DRT)** to ensure they do not reach a pre-defined threshold of 25%. If this threshold is reached, the DRT will have the discretion to change to another dose/schedule tested in phase 1**b** part 1, based on the totality of the available data. The details of DLT boundaries are provided in Section 8.1.

Study Design and Treatment Schema

Figure 1. Study Design and Treatment Schema

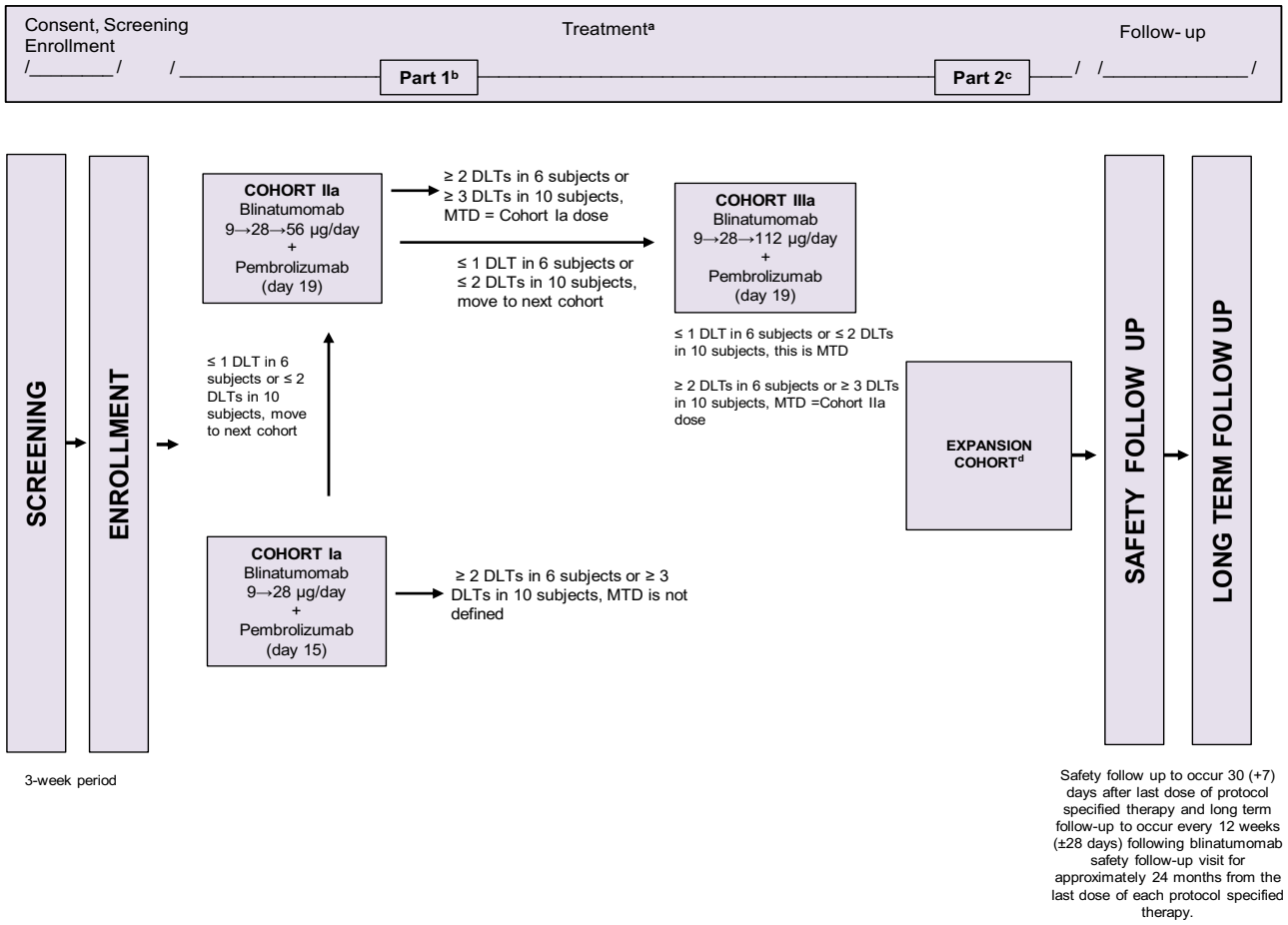

Figure Legend present on next page

DLT = dose limiting toxicity; MTD = maximum tolerated dose. First cycle of blinatumomab will be 8 weeks in duration, followed by a 28-day (± 3 days) blinatumomab treatment-free interval. A second consolidation cycle of blinatumomab will be 28 days in duration at the same dose as the first cycle, starting at 9 μg/day with weekly dose escalations until the target dose is reached, if subject has stable disease or partial/complete remission after cycle 1. Pembrolizumab will be started on study day 15 for cohort Ia, and study day 19 for cohorts IIa and IIIa, and administered Q3 weeks until disease progression for up to 35 cycles. **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1 of protocol). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events and if blinatumomab was interrupted, no > grade 1 CRS and/or neurologic events. The cohort name has been updated to be in sequential order, retaining the historical "a" in the cohort name (ie, cohorts Ia, IIa, IIIa) from previous protocol naming convention.**

[a] For cohorts Ia, IIa and IIIa, the DLT observation period will begin on the same day as the first dose of pembrolizumab (day 15 for Ia and day 19 for IIa and IIIa) and will continue for 42 days. **For part 2, the DLT observation period will be determined by cohort chosen in Part 1 and Part 2 expansion.** A dose level review team (DLRT) will review the available data to determine if blinatumomab is safe and tolerable as defined by DLT criteria **and general clinical judgement. Based on the totality of the data, the DLRT may recommend to declare MTD, to escalate to the next dose level, to expand a cohort to a maximum of 10 subjects if the collection of more data is deemed warranted, or to adjudicate the DLT criteria.**

[b] Part 1: To determine maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab. The MTD will be defined as the dose level at which ≤ 1 **DLT in** 6 subjects **or ≤ 2 DLTs in 10 subjects** experience a Dose limiting toxicity (DLT).

[c] Part 2: Expansion cohort to estimate the efficacy of the combination of blinatumomab and pembrolizumab. Dosing will be determined based on the MTD of blinatumomab established in part 1. **Dose limiting toxicities and efficacy will be monitored by the Data Review Team to ensure they do not reach a pre-defined threshold of 25%.**

[d] Dosing for the Part 2 expansion cohort will be based on the safety of the combination of blinatumomab and pembrolizumab and the MTD of blinatumomab in Part 1.

3.2 Sample Size

Part 1:

A rolling 6 dose design will be used. An additional 4 subjects per cohort can be enrolled to further evaluate safety and PK data if needed. There will be a minimum of 6 subjects and a maximum of **30** subjects enrolled.

Part 2:

Forty subjects will be enrolled in Part 2. With 40 subjects, the 95% exact confidence interval (Clopper and Pearson, 1934) for the estimate of ORR can be calculated. The 95% confidence intervals for some ORRs are shown in the table below.

Table 1. Estimated 95 % Confidence Interval for ORR

ORR	95% Confidence Interval
0.40	**(0.25, 0.57)**
0.45	**(0.29, 0.61)**
0.50	**(0.34, 0.71)**
0.55	**(0.38, 0.71)**
0.60	**(0.43, 0.75)**

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

- Incidence of DLTs

4.1.2 Secondary Endpoints

- **Objective response** (including CR and PR) by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first** 12 weeks since starting blinatumomab **and during the treatment period**.
- **Complete response** by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first** 12 weeks since starting blinatumomab **and during the treatment period.**
- PFS
- OS
- Duration of response (DOR) **for subjects with** OR, (ie, CR and PR) by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first** 12 weeks **since** starting blinatumomab
- Blinatumomab PK parameters
- Pembrolizumab PK parameters

4.1.3 Safety Endpoints

- Incidence and severity of adverse events

4.1.4 Exploratory Endpoints

- **Tumor** PD-L1 expression **will be assessed pre-treatment and on treatment to explore potential correlation with clinical outcomes**
- Changes in Lymphocytes (B-cell, T-cell populations, NK cells) and leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) in peripheral blood
- Peripheral blood cytokine levels
- Minimal residual disease (MRD) by NGS after cycle 1 of blinatumomab

5. Hypotheses and/or Estimations

The overlying hypothesis is that blinatumomab in combination with pembrolizumab will be tolerable in r/r DLBCL.

6. Definitions

6.1 General Definitions

Age at Enrollment

Subject age at enrollment will be collected in years in the clinical database.

Baseline

For the analysis of all endpoints, baseline will be defined as the value measured on day 1 of the first cycle of blinatumomab. The protocol specifies that procedures and labs on day 1 should be completed before the initiation of any protocol-specified therapy which will be the assumption in the analysis unless the time of the assessment is recorded. If a day 1 value is not available, the most recent value before the day of the start of any protocol-specified therapy may be used.

Cumulative Dose of Blinatumomab, Pembrolizumab

Blinatumomab: The cumulative dose in µg is defined as the following with summation over infusions:

$\sum$ (Duration of infusion (days) for each dose received x dose received [µg])

Pembrolizumab: The cumulative dose in mg is defined as the following with summation over infusions:

$\sum$ (Duration of infusion (days) for each dose received x dose received [mg])

Cumulative dose will be calculated within a cycle and across all cycles.

Death Date

For subjects who die during the study, the death date will be recorded on the event, end of study and survival status CRF. The earliest date will be used if the dates are inconsistent among these CRF pages. For deaths collected after a subject has ended study (eg, through public records in countries where permitted), the death date will be recorded on the long term follow-up page.

Dose limiting toxicity (DLT)

The occurrence of any of the toxicities in the Appendix E of the protocol will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to study drug administration.

DLT Evaluable

To be DLT evaluable, subjects must meet one of the following criteria during DLT evaluation period:

- The subject experienced a DLT;

OR

- The subject was removed from treatment for an adverse event/toxicity **that is not a DLT, if the subject has been exposed to both investigational products for at least 12 days since pembrolizumab initiation with blinatumomab at the target dose;**

OR

- The subject was removed from treatment for reasons other than an adverse event/toxicity (ie, disease progression), and the subject has **been exposed to both investigational products for** at least 12 days **since pembrolizumab initiation** with blinatumomab at the target dose;

OR

- The subject did not experience a DLT and completed the DLT **evaluation** period.

Duration of Blinatumomab/Pembrolizumab

Blinatumomab/ Pembrolizumab: For each infusion episode within a cycle, the duration of exposure will be calculated by subtracting the start date and time from the stop date and time. If either a start or stop time is missing, only the date portion will be used in calculating the duration of a specific infusion. For each cycle, the duration will be last date minus first date plus 1 of infusion. For the entire study, the duration will be the sum of the durations across cycles. The duration will be rounded to the nearest day.

Event of Clinical Interest (ECI)

Selected non-serious and serious adverse events are known as ECI and must be reported within 24 hours to the sponsor. The ECI for this trial includes

- An overdose of blinatumomab or pembrolizumab (see Protocol Section 6.2.1.1 and Section 6.2.2.1)
- Hepatic disorder (See protocol section 9.1.4)

Events of interest (EOI)

Events of interest (EOI) will be based on search strategies defined by Standard MedDRA Queries (SMQs) or Amgen MedDRA Queries (AMQs).

End of Investigational Product (IP) Administration Date

End of IP Administration for subjects who had blinatumomab or pembrolizumab is defined as the last infusion of blinatumomab/ pembrolizumab reported on the End of IP Administration CRF.

Enrollment Date

Enrollment Date is defined as the date of enrollment collected on the CRF.

Investigational Product

Amgen Investigational Product: refers to blinatumomab

Non-Amgen Investigational Product: refers to pembrolizumab

Last Dose Date of Blinatumomab/ Pembrolizumab

This is the stop date of the last infusion of blinatumomab/pembrolizumab administration reported on the Investigational Product Administration CRF.

Treatment period

Treatment period will be from study day 1 to 30 days after last dose of either blinatumomab/ pembrolizumab administration reported on the Investigational Product Administration CRF.

Prior Salvage Regimens

Prior salvage regimens are those medications recorded on the prior anti-cancer therapies CRF where the line of therapy field indicates 2nd or higher line therapy.

Relative Dose Intensity at the Target Dose

Relative dose intensity at the target dose is the actual exposure duration at target dose divided by planned duration of target dose, which is 49 days for cohort Ia, and 42 days for cohort IIa and IIIa in cycle 1; and 21 days for cohort Ia, and 14 days for cohort IIa and IIIa in cycle 2. Subjects who didn't reach the target dose are considered having actual exposure duration as 0.

Study Day

Study Day 1 is defined as the day of first dose of blinatumomab.

And Study Day is defined as:

Pre study day 1: study day= (date – date of study day 1)

Post study day 1: study day= (date - date of study day 1) + 1

Subject Level End of Study (EOS) Date

End of Study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Treatment Emergent Adverse Event (AE)

Treatment emergent adverse event refers to an adverse event that starts on or after first dose of blinatumomab up to and including 30 days after the end of blinatumomab or pembrolizumab whichever is later. It is indicated by a flag whether an event start before first dose of blinatumomab on the Event CRF page. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

Treatment Emergent Disease-related Event (DRE)

Treatment emergent disease-related event refers to a disease-related event that starts on or after first dose of blinatumomab up to and including 30 days after the end of blinatumomab or pembrolizumab whichever is later. It is indicated by a flag whether an event start before first dose of blinatumomab on the Event CRF page.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

Treatment Emergent Event of Clinical Interest (ECI)

ECI is defined in Section 9.1.4 of the protocol. Treatment emergent ECI refers to an ECI that starts on or after first dose of blinatumomab up to and including 30 days after the end of blinatumomab or pembrolizumab whichever is later.

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up) as applicable.

6.2 Efficacy Endpoints

Complete **Response** (CR) Rate **by the Lugano Classification**

Complete **response** rate **by the Lugano Classification** is the proportion of subjects who have achieved complete **response** by **the Lugano Classification (Cheson et al, 2014) during the first** 12 weeks since starting blinatumomab **and during the treatment period** among all subjects in the respective analysis set.

Complete **Response** (CR) Rate **by the Revised Response Criteria**

Complete **response** rate **by the Revised Response Criteria** is the proportion of subjects who have achieved complete **response** by **the Revised Response Criteria (Cheson et al, 2007) during the first** 12 weeks since starting blinatumomab **and during the treatment period** among all subjects in the respective analysis set.

Duration of Response (DOR) by **Lugano Classification**

Duration of response will be calculated only for subjects who achieve an OR (ie, CR or PR) by **Lugano Classification (Cheson et al, 2014)** criteria **during the first** 12 weeks **since** starting blinatumomab. The duration will be calculated from the date a response, CR or PR, is first achieved until the earliest date of a disease assessment indicating a disease progression or death, whichever occurs first. **For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Lugano Classification will be used.** Subjects who do not have a relapse event will be censored on their last **radiological non-missing evaluable tumor assessment date**.

Duration of Response (DOR) by Revised Response Criteria (Cheson et al, 2007)
Duration of response will be calculated only for subjects who achieve an OR (ie, CR or PR) by Revised Response Criteria (Cheson et al, 2007) criteria during the first 12 weeks since starting blinatumomab. The duration will be calculated from the date a response, CR or PR, is first achieved until the earliest date of a disease assessment indicating a disease progression or death, whichever occurs first. For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Revised Response Criteria (Cheson et al, 2007) will be used. Subjects who do not have a relapse event will be censored on their last radiological non-missing evaluable tumor assessment date.

Objective Response by the Lugano Classification
Objective response (including CR and PR) by the Lugano Classification is determined by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab and during the treatment period.

Objective Response by the Revised Response Criteria
Objective response (including CR and PR) by the Revised Response Criteria is determined by the Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period.

Objective Response Rate (ORR) **by the Lugano Classification**

Objective response rate (ORR) **by the Lugano Classification** is the proportion of subjects who have achieved either a CR or a PR among subjects by **the Lugano Classification (Cheson et al, 2014)** during the first 12 weeks since starting blinatumomab **and during the treatment period** in the respective analysis set.

Objective Response Rate (ORR) **by the Revised Response Criteria**

Objective response rate (ORR) **by the Revised Response Criteria** is the proportion of subjects who have achieved either a CR or a PR among subjects by **the Revised Response Criteria (Cheson et al, 2007)** during the first 12 weeks since starting blinatumomab **and during the treatment period** in the respective analysis set.

Overall Survival (OS)

The overall survival will be calculated as the time from the date of first dose of blinatumomab until death due to any cause. Subjects who are alive at the date that triggers the analysis will be censored at the date last known to be alive.

Progression Free Survival (PFS) by **Lugano Classification**

The PFS will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. **For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Lugano Classification will be used.** Subjects who are alive and did not have progression will be censored at the last **radiological non-missing evaluable** tumor assessment date.

Progression Free Survival (PFS) by Revised Response Criteria

The PFS will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Revised Response Criteria will be used. Subjects who are alive and did not have progression will be censored at the last radiological non-missing evaluable tumor assessment date.

6.3 PRO Endpoint

Not Applicable.

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set includes all subjects who received blinatumomab.

7.2 Safety Analysis Set

Safety analysis set is same as the full analysis set.

7.3 Responder Analysis Set

The responder analysis set includes all subjects who had CR or PR within 12 weeks after starting blinatumomab.

7.4 DLT Analysis Set

DLT analysis set includes all subjects who are DLT-evaluable.

7.5 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set for blinatumomab includes all subjects who received any infusion of blinatumomab or pembrolizumab and have at least 1 pharmacokinetic sample collected.

7.6 Pharmacodynamic Analysis Set

The cytokine analysis set includes all subjects who receive any infusion of blinatumomab and have at least 1 **pharmacodynamic** sample collected.

For other biomarker analysis set include all subjects who received blinatumomab and pembrolizumab and have at least one biomarker sample collected.

7.7 Interim Analyses Set(s)

Interim analysis set will include all subjects at the interim analysis.

8. Interim Analysis and Early Stopping Guidelines

8.1 Interim Analyses

DRT will conduct evaluations of efficacy for ORR by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab and safety for DLT rate to assess if the threshold for early trial termination has been reached.

Table 2 **shows the efficacy stopping rules using a Bayesian approach to potentially terminate the study if the posterior probability that ORR is less than 50% is > 80%. The stopping boundaries assume a prior beta distribution (1, 1). The operating characteristics in Table 3 provide the probability of stopping the trial early for given hypothetical true ORR.**

Table 2. Efficacy Stopping Boundary With Batch Size of 10 Subjects, Posterior Probability of 80% and ORR of 50%

Number of evaluable subjects	Stop study if observing these many responders
10	**≤ 3**
20	**≤ 8**
30	**≤ 12**
40	**Always stop**

Table 3. Operating Characteristics With Batch Size of 10 Subjects

True ORR	Prob of Stopping Early	Average Sample Size
0.40	**70%**	**23**
0.45	**52%**	**27**
0.50	**34%**	**32**
0.55	**19%**	**19**
0.60	**9%**	**38**

Table 4 **shows the safety stopping rules using** a Bayesian approach to terminate the study if the posterior probability that the DLT rate is greater than 25% is > 90%. The stopping boundaries assume a prior beta distribution (0.50, 1.50). The evaluations could occur more frequently if necessary, to address emerging safety concerns. The operating characteristics in Table 5 provide the probability of stopping the trial early for given hypothetical true DLT rates.

Table 4. Safety Stopping Boundary With Batch Size of 10 Subjects, Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects	Stop study if observing these many DLTs
10	**≥ 5**
20	**≥ 8**
30	**≥ 11**
40	**Always stop**

DLT = dose limiting toxicity

Table 5. Operating Characteristics With Batch Size of 10 Subjects

True DLT Rate	Prob. of Stopping Early	Average Sample Size
0.20	**6%**	**38**
0.25	**17%**	**36**
0.30	**36%**	**32**
0.35	**57%**	27
0.40	**76%**	22

DLT = dose limiting toxicity; prob = probability

8.2 Dose Level Review Team (DLRT) and Data Review Team (DRT)

DLRT:

The DLRT will review safety data from each cohort in part 1 to determine if the combination of blinatumomab and pembrolizumab is safe and tolerable as defined by DLT criteria and general clinical judgement, taking into account a general benefit risk assessment. Pharmacokinetic data may be reviewed, if available.

Based on the totality of the data, the DLRT may recommend to declare MTD, to escalate to the next dose level, to expand a cohort to a maximum of 10 subjects, if the collection of more data is deemed warranted, or to adjudicate the DLT criteria.

The DLRT will meet to review the safety data, when any of the following criteria are met:

- In 2 or more **out of 6 subjects, a DLT has been reported or in 3 or more out of 10** subjects, a DLT has been reported in a cohort
- 6 subjects are enrolled in a cohort and all subjects have completed the DLT observation period
- In the event that a cohort is expanded to 10, DLRT **will** also meet after all subjects have completed DLT observation period

The DLRT will consist of, at minimum, members from the Amgen study team including at least one clinician, one safety representative, members outside the Amgen study team including at least one representative of the Merck study team, and one investigator participating in the study who has recruited subjects into the cohort under review. A cohort may be expanded by DLRT recommendation in the case that the data suggests a change to the anticipated risk/benefit profile, warranting collection of further data at the blinatumomab target dose.

In part 2, DRT will meet after every set of 10 subjects who become DLT evaluable.

A DRT is a group, internal to Amgen but external to the product team, that reviews accumulating data from the ongoing clinical trial to evaluate overall benefit and

risk. The DRT includes a clinician, a safety physician, and a biostatistician. Experts external to Amgen may be included if needed. Membership, procedures and meeting timing will be described in detail in the study DRT charter.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. The database will be subject to edit checks outlined in the data management plan by Amgen Clinical Data Management (CDM) department. Any outstanding data issues will be communicated to CDM for resolution before the database is locked.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE Clinical database.

An Analysis Dataset for PK Concentrations (ADPC) will be provided to the appropriate Clinical Pharmacology Modeling and Simulation CPMS representative from Global Biostatistical Sciences.

9.3 Handling of Missing and Incomplete Data

Subjects without tumor response assessments will be considered as non-responders. Otherwise, only non-missing data will be analyzed. No other missing value replacement procedure will be deployed for clinical data. The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix A. Handling of missing or incomplete data for exposure-response analysis will be described in the E-R supplemental SAP (SSAP) or associated documents to support population PK/PD dataset generation and E-R analysis.

9.4 Detection of Bias

If applicable, the methods to detect bias are described in the analyses of particular endpoints.

9.5 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be

discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

PK serum concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

9.6 Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. If the assumptions for the distributional characteristics are not met, these will be described, and further analyses may be carried out using data transformations or alternative analysis methods. The use of transformations or alternative analysis methods will be justified in the final study report.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained; and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The analysis will be performed by cohorts for part 1. The analyses for part 2 will combine subjects in part 2 and the cohort in part 1 with selected dose for part 2 unless specified otherwise. The analyses will be performed on the Full Analysis Set unless specified otherwise.

Continuous variables will be summarized by the non-missing sample size n, mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM

proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934). Pharmacokinetics will be performed by noncompartmental analysis. Pharmacodynamic samples will be summarized by descriptive statistics.

Relationships among drug exposures and efficacy, safety, and biomarkers may be explored if the data are sufficient.

10.2 Subject Accountability

The number (and percent) of subjects who were screened, received blinatumomab and pembrolizumab and complete the study will be summarized. The number (and percent) of subjects who discontinue each treatment and the study and their reasons for discontinuation will be summarized.

10.3 Important Protocol Deviations

Categories for Important Protocol Deviations (IPDs) are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age group, sex, race, and ethnicity) and baseline disease characteristics will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple races as well as by combination of races.

The baseline characteristics to be summarized include:

- Age
  - age group: < 65, 65-74, ≥ 75
  - age as continuous variable
- Sex: Male, Female
- Race
  - American Indian or Alaska Native
  - Asian
  - Black (or African American)
  - Native Hawaiian or other Pacific Islander
  - White
  - Other

- Geographic region
  - US/Canada
  - Asia
  - Europe
  - Rest of the world
- aaIPI: Low (0), Low-Intermediate (1), High-Intermediate (2), High (3)
- Primary disease status: Relapsed, Refractory
- Prior HSCT: Yes, No
- Extranodal disease: Yes, No.
- Cell of Origin Determination: GCB, Non-GCB, ABC, Not done
- Bcl-2 rearrangement status: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done
- Bcl-2 overexpression status: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done
- Bcl-6 rearrangement: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done.
- Bcl-6 overexpression: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done.
- C-myc rearrangement status: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done
- C-myc overexpression status: Normal, Rearranged, Overexpressed, Not Overexpressed, Not done
- Double hit: Yes, No (Yes is defined by both C-myc and Bcl-6 overexpression and rearrangement are Yes; otherwise No)
- Triple hit: Yes, No, (defined as 'Yes' if all of Bcl-2, Bcl-6 and C-myc rearrangement are 'Yes', else 'No'.)
- Double high expressor: Yes, No, (defined as 'Yes' if Two of Bcl-2, Bcl-6, C-myc overexpression are Yes', else 'No'.)
- Triple high expressor: Yes, No, (defined as 'Yes' if all of Bcl-2, Bcl-6, C-myc overexpression are Yes', else 'No'.)

10.5 Efficacy Analyses

The efficacy endpoints are ORR, CR, PFS, OS and DOR.

The percentage of subjects with an objective response (CR/ PR) using **the Lugano Classification; and an objective response (CR/ PR) using Revised Response Criteria during** the first 12 weeks since starting blinatumomab **(for part 2 and the cohort in part 1 with selected dose only)** and during the **treatment period** will be summarized with an exact **2-sided** binomial 95% confidence interval **using Full**

Analysis Set. Subjects missing post baseline disease assessments will be considered not to have achieved an objective response.

The KM summaries will be performed for PFS and OS. K-M quartiles along with 2-sided 95% CIs, the number of subjects censored and the number of subjects with events will be provided **using FAS**. The KM summaries of DOR **will** be performed using Responder Analysis Set.

The exploratory endpoint minimal residual disease (MRD) by NGS after cycle 1 of blinatumomab will be summarized with descriptive statistics by treatment cohort using full analysis set.

10.6 Safety Analyses

10.6.1 DLT Summary

The DLT criteria are defined in the Appendix E of the protocol.

Incidence rates of DLTs and corresponding exact binomial 95% CIs will be summarized for DLT evaluable subjects.

10.6.2 Adverse Events and Disease Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or later will be used to code all events categorized as adverse events (AEs) or disease-related events (DREs) to a system organ class and a preferred term. AEs of interest (EOI) categories will be based on search strategies defined by Medical Coding. **Treatment emergent adverse event refers to an adverse event that starts on or after first dose of blinatumomab up to and including 30 days after the end of blinatumomab or pembrolizumab whichever is later.**

Subject incidence of all, serious, grade 3 and above, leading to withdrawal of investigational product, leading to interruption of investigational product, fatal, treatment-related, **treatment-related serious, and treatment-related grade 3 and above** treatment-emergent adverse events **(including DREs)** will be tabulated by system organ class and preferred term in descending order of frequency **for highest dose group**.

Treatment-emergent events of interest (EOIs) will be summarized by EOI category and preferred term. In addition, for each EOI category, the subject incidence of all, serious, **grade 3 and above, grade 4 and above**, fatal, leading to withdrawal of investigational product, leading to interruption of investigational product will be summarized. **Time to onset, duration, number of selected EOIs will also be summarized.**

Additionally, treatment emergent DREs and fatal DREs will be summarized by system organ class and preferred term in descending order of frequency **for highest dose group**. Subject incidence of ECIs will be summarized by ECI category and preferred term in descending order of frequency **for highest dose group.**

Subgroup analyses of treatment-emergent adverse events will be presented for age-group (< 65, 65-74, ≥ 75), and gender by system organ glass and preferred term in descending order of frequency for highest dose group.

Subject listings of Serious AEs, Fatal AEs and Deaths will be provided. Analyses will be performed based on Safety Analysis Set.

10.6.3 Laboratory Test Results

Summary statistics over scheduled visits for actual values, changes from baseline of selected laboratory parameters below will be presented for subjects in the **Safety** Analysis Set.

1. **Corrected** Calcium
2. Magnesium
3. Total bilirubin
4. Direct bilirubin
5. Alkaline phosphatase
6. AST (SGOT)
7. ALT (SGPT)
8. Amylase
9. Lipase
10. Hemoglobin
11. Platelets
12. Neutrophils
13. Lymphocytes
14. LDH
15. Immunoglobulins (IgG, IgA, IgM)
16. Fibrinogen

Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided.

The subject incidence of potential cases of Hy's Law will be summarized.

10.6.4 Vital Signs

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will **be** summarized based on **Safety** Analysis Set.

10.6.5 Physical Measurements

Not Applicable

10.6.6 Electrocardiogram (ECG)

Not Applicable

10.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti blinatumomab antibodies (binding and if positive, neutralizing) and anti-pembrolizumab antibodies at any time will be tabulated.

10.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab and pembrolizumab. The number of cycles initiated, completed, discontinued, and re-started of blinatumomab and pembrolizumab will be summarized. **If a subject completed 85% of planned days on target dose, he/she is considered as completing a cycle**. In addition, the duration of therapy will be summarized by cycle and overall. **Relative dose intensity at the target dose will be calculated. It is the actual exposure duration at target dose divided by planned duration of target dose, which is 49 days for cohort Ia, and 42 days for cohort IIa and IIIa in cycle 1; and 21 days for cohort Ia, and 14 days for cohort IIa and IIIa in cycle 2. Subjects who didn't reach the target dose are considered having actual exposure duration as 0. Relative dose intensity at the target dose will be summarized by cycle.** The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reasons for modification will be summarized. **Analysis will be performed based on Safety Analysis Set.**

10.6.9 Exposure to Concomitant Medication

The number and percent of subjects receiving concomitant medications from study day 1 through blinatumomab or pembrolizumab safety follow-up, whichever is later will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary. In addition, the number and proportion of subjects receiving

anti-cancer therapies during long term follow-up will be summarized **using Safety Analysis Set.**

10.6.10 Pharmacokinetic Analysis of Blinatumomab

Blinatumomab serum samples will be taken as listed in Schedule of Assessment of protocol. All data for PK analyses will be extracted from a secure folder and were mapped via the SAS_CDISC_v2 clinical connector into the Pharsight Knowledgebase Server (PKS) system version 4.0.3 (Pharsight®, St. Louis, MO).

Blinatumomab pharmacokinetic analysis will be performed using Phoenix WinNonlin v.6.4 software on Citrix (Pharsight®, St. Louis, MO) as part of the validated PKS system on individual serum blinatumomab concentrations to estimate the following PK parameters:

- The steady state serum concentration (C_{ss}) of cycle 1 summarized as the observed concentrations collected during continuous IV infusion by dose levels.
- Systemic clearance (CL) calculated as $CL=R_0/C_{ss}$; where R_0 is the infusion rate (μg/hr) and C_{ss} is the dose normalized average C_{ss}.

Nominal times were used for presenting data in tables. Blinatumomab concentrations below the lower limit of quantification (LLOQ, 50 pg/mL) were set to zero before data analysis. All individual PK parameters and descriptive statistics are presented to 3 significant figures, except for CV%, which was reported to 1 decimal place.

PK parameters such as steady state concentration (Css) will be estimated for patients who have evaluable PK data. Summary statistics, including mean, standard deviation, CV%, median, range (Minimal, Maximal), geometric mean and CV% of geometric mean will be computed for each pharmacokinetic parameter and grouped by dose, and treatment Phase. Individual concentration-time data will be tabulated and presented in PK appendix. Mean concentration-time profiles for each cohort may be provided, if sufficient data are available. **Analyses will be performed based on Pharmacokinetic Analysis Set.**

10.6.11 Pharmacokinetic Analysis of Pembrolizumab

Pembrolizumab serum samples will be taken as listed in Schedule of Assessment of protocol. Pembrolizumab exposure parameters (eg, concentrations at the end of IV infusion and steady state trough concentrations) will be estimated for subjects who have evaluable PK data. Summary statistics, including mean, standard deviation, CV%, median, range (Minimal, Maximal), geometric mean and CV% of geometric mean will be

computed for each pharmacokinetic parameter by treatment cycles. Individual concentration-time data will be tabulated and presented in PK appendix. Mean concentration-time profiles may be provided, if sufficient data are available. **Analyses will be based on Pharmacokinetic Analysis Set**

10.6.12 Pharmacodynamic Analysis

Blood samples for biomarker analysis will be taken as described in the Schedule of Assessment of protocol. The cytokine levels over time will be analyzed with summary statistics by treatment period and treatment cohort. The changes in Lymphocytes (B-cell, T-cell populations, NK cells), leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) and Tumor PD-L1 expression over time will be summarized with descriptive statistics by treatment period and treatment cohort. Other analysis may be performed as appropriate. There will be a separate biomarker SSAP developed with a molecular scientist.

Merck biomarker lead will define analysis related to pembrolizumab and PD-L1.
Analyses will be based on Pharmacodynamic Analysis Set.

10.6.13 Exposure Response Analysis

PK data of blinatumomab may be subjected to exploratory population PK analysis with data from multiple studies. Nonlinear mixed effects modeling will be used for the analysis. Effect of covariates on exposure will be determined. These may include, age, body weight, body surface area, renal function, liver function, sex and selected baseline lab values. Other covariates may be analyzed as needed. Individual blinatumomab concentration data at time of interest may be used for the exposure response analysis.

Exposure-response relationships for selected efficacy and safety endpoints may be assessed as appropriate. The objectives and methodology of the exposure-response analysis will be provided in an E-R SSAP.

11. Changes From Protocol-specified Analyses

Because the decision was made not to proceed with Part 2 of the study. The primary analysis will now occur after the last subject in Part 1 has had an opportunity to complete response assessment during first 12 weeks since starting blinatumomab.

Other changes include modifications of the definitions to the following endpoints.

Secondary Endpoint (Per protocol):

Duration of response (DOR) for subjects with OR, (ie, CR and PR) by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab.

Changes from protocol:

Duration of response (DOR) for subjects with OR, (ie, CR and PR) by the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab.

PFS definition (Per protocol):

The PFS will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Lugano Classification will be used. Subjects who are alive and did not have progression will be censored at the last radiological non-missing evaluable tumor assessment date. Progression free survival for subjects who were enrolled in dose cohorts that were not selected for the extension cohort will not be calculated.

Changes from protocol:

Progression Free Survival (PFS) by Lugano Classification:

The PFS will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Lugano Classification will be used. Subjects who are alive and did not have progression will be censored at the last radiological non-missing evaluable tumor assessment date.

Progression Free Survival (PFS) by Revised Response Criteria:

The PFS will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET-CT using Revised Response Criteria will be used. Subjects who are alive and did not have progression will be censored at the last radiological non-missing evaluable tumor assessment date.

12. Literature Citations / References

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13. Prioritization of Analyses

Not Applicable.

14. Data Not Covered by This Plan

Not Applicable.

15. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Handling Incomplete Dates and Missing Dates for Adverse Events and Concomitant Medications.

The following data will be imputed using the following algorithm:

- Adverse Events
- Concomitant Medications

Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	Missing
Partial: *yyyymm*	= **1st dose** *yyyymm*	2	1	2	1	n/a	1	1
	≠ **1st dose** *yyyymm*		2		2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	**3**	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing stop dates:

Initial imputation

- For partial stop date mmyyyy, impute the last of the month.
- For partial stop date yyyy, impute December 31 of the year.
- For completely missing stop date, do not impute.

- If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
- If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie. set the stop date as missing).

Imputation rules for partial or missing death dates:

- If death year and month are available but day is missing:
- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

  If both month and day are missing for death date or a death date is totally missing, do not impute.

Appendix B. Reference Values/Toxicity Grades

Laboratory Values

Safety laboratory values below a distinct limit (eg, detection limit, documented as "< [limit]") will be substituted by half of the limit and values above a distinct limit (documented as "> [limit]") will be substituted by the limit itself for all analyses. A Grade (based on CTC AE version 4.0 [v4.03: June 14, 2010]) will be assigned to each laboratory result as detailed in Table 6. Depending on the toxicity definition, the same result may be assigned to two grading for deviations towards higher or lower values. In case no lower limit of normal is provided for the absolute lymphocyte, neutrophils or leukocyte counts it will not be differentiated between grade 1 and grade 0 results for these parameters. Values not meeting any of the criteria will be assigned a grade 0.

Grading of Select Laboratory Parameters

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocytes [G/L]	0.8 - < LLN	0.5 - < 0.8	0.2 - < 0.5	< 0.2
Neutrophils [G/L]	1.5 - < LLN	1.0 - < 1.5	0.5 - < 1.0	< 0.5
Leukocytes [G/L]	3.0 - < LLN	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets [G/L]	75 - < LLN	50 - < 75	25 - < 50	< 25
Hemoglobin [g/L]*	100 - < LLN	80 - < 100	65 - < 80	< 65
Albumin [g/L]	30 - < LLN	20 - < 30	< 20	not defined
AST*	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
ALT *	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
GGT	> ULN – 2.5*ULN	>2.5*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
Bilirubin	> ULN – 1.5*ULN	>1.5*ULN – 3*ULN	> 3*ULN – 10*ULN	> 10*ULN
Fibrinogen^	%change of BL <25% or 0.75*LLN - < LLN	25%- <50% of BL or < 75*LLN – 0.5*LLN	50% - <75% of BL or < 0.5* LLN – 0.25*LLN	>= 75% of BL or < 50mg/dL or < 0.25*LLN

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
Calcium [mmol/L]*	2.0 - < LLN	1.75 - < 2.0	1.5 - < 1.75	< 1.5
Potassium [mmol/L]*	not defined	3.0 - < LLN	2.5 - < 3.0	< 2.5
Lipase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN
Amylase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN

BL baseline value, LLN: Lower limit of normal, ULN: Upper limit of normal
*** Clinical criteria from CTC AE 4.0 grading were not considered in order to assign grades**
^ In case of conflicting criteria the higher grade will be assigned, % change only used when baseline is <LLN