Statistical Analysis Plan

A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-689 in Patients with Relapsed or Refractory Lymphoma

Protocol Number:	2018-689-00US1
Amendment number:	5
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Phase:	Phase I
Sponsor:	HUTCHMED Limited. Address: Building 4, Lane 720 Cailun Road, Pilot Free Trade Zone, China (Shanghai), 201203 Tel: PPD Fax: PPD
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Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

APPROVAL SIGNATURES

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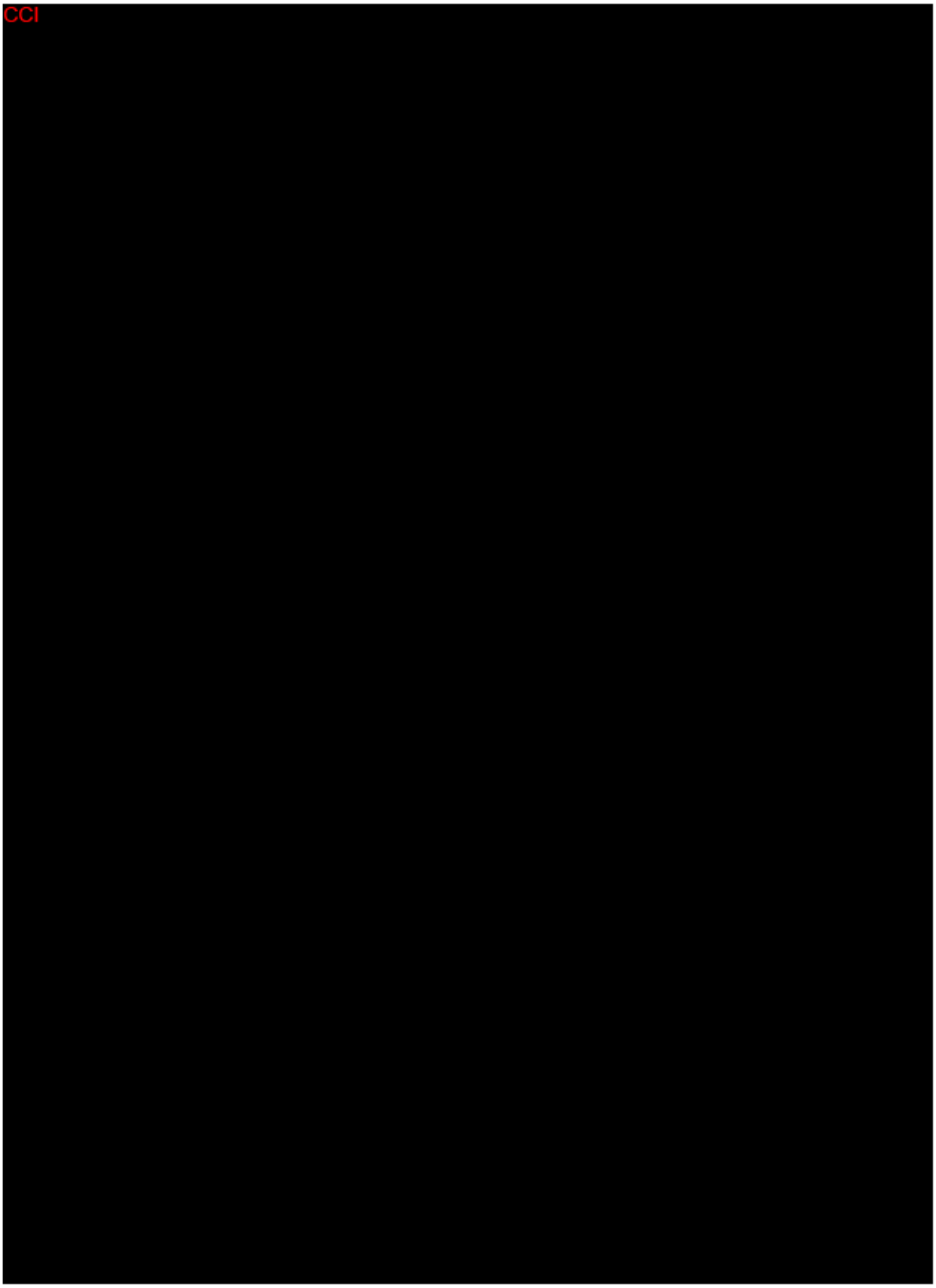
MODIFICATION HISTORY

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1. LIST OF ABBREVIATIONS

Terms and Abbreviations	Definition
AE	Adverse Event
AESI	Adverse Events of Special Interest
CBCL	Cutaneous B-cell Lymphoma
CBR	Clinical Benefit Rate
CFB	Change from Baseline
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CRi	Complete Response with Incomplete Marrow Recovery
CRF	Case Report Form
CTMS	Clinical Trial Management System
DEAS	DLT Evaluable Analysis Set
DLT	Dose-limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FL	Follicular Lymphoma
ICF	Informed Consent Form
LDH	Lactate Dehydrogenase
LPL/WM	Lymphoplasmacytic Lymphoma / Waldenström's Macroglobulinemia
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
mTPI-2	Modified Toxicity Probability Interval Scheme-2
MTD	Maximum Tolerated Dose
MZL	Marginal Zone Lymphoma
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin Lymphoma
nPR	Nodular Partial Response
ORR	Objective Response Rate
PCFB	Percentage Change from Baseline

PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PR-L	Partial Response with Lymphocytosis
PT	Preferred Term
PTCL	Peripheral T-cell Lymphoma
QD	Once Daily
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SOC	System Organ Class
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TTR	Time to Response
VGPR	Very Good Partial Response
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Note: Standard units such as mg and mL as used in the text are not included in the abbreviations list.

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 2018-689-00US1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. The pharmacokinetics (PK) part will not be documented in this SAP and a separate analysis plan for PK analysis will be developed.

This statistical analysis plan (SAP) is based on protocol amendment 5 (dated 08Dec2022) and CRF version 6 (dated 13Jan2023).

Per protocol amendment 5, the end of the study is defined as 18 months after the last patient has been enrolled in the study or all patients have discontinued the study treatment, whichever comes earlier. CCI [redacted].

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. PRIMARY OBJECTIVE

DOSE ESCALATION PHASE (STAGE 1)

The primary objective of the dose escalation phase (Stage 1) is to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma.

DOSE EXPANSION PHASE (STAGE 2)

The primary objective of the dose expansion phase (Stage 2) is to further evaluate safety and tolerability of HMPL-689 at MTD in patients with relapsed, refractory, or resistant lymphoma.

3.2. SECONDARY OBJECTIVES

The secondary objectives are (for both stages):

- To assess preliminary efficacy of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma overall and by lymphoma sub-types as assessed by investigator.
- To characterize PK parameters of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma at both dose escalation and dose expansion stages.
- To evaluate the effect of HMPL-689 on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals.

Table 1 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary – Dose Escalation	To determine MTD and/or RP2D of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma	• Incidence of DLTs • Safety (including but not limited to TEAEs, treatment-related adverse events [TRAEs], SAEs, treatment-related SAEs [TRSAEs], and lab abnormalities)
Primary – Dose Expansion	To further evaluate safety and tolerability of HMPL-689 at MTD in patients with relapsed, refractory, or resistant lymphoma	• Safety, including TEAEs and TRAEs
Secondary	To assess preliminary efficacy of HMPL689 in patients with relapsed, refractory, or resistant lymphoma overall and by lymphoma sub-types as assessed by investigator	• ORR • TTR • DoR • CBR • PFS
	To characterize PK parameters of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma at both dose escalation and dose expansion stages	• Concentration-time profiles and PK parameters after single dose and at steady state
	To evaluate the effect of HMPL-689 on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals	• QTc interval and HMPL-689 concentration

Abbreviations: CBR = clinical benefit rate; DLT = dose-limiting toxicity; DoR = duration of response; MTD = maximum tolerated dose; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event; TTR = time to response.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a Phase 1, open-label, multicenter study of HMPL-689 administered orally to patients with relapsed, refractory, or resistant lymphoma.
This study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). Both Stage 1 and Stage 2 include the following periods: screening period, treatment period, safety follow-up period, and extended progression free survival (PFS) follow-up period, if applicable.
The study duration is estimated to be approximately 48 months.

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[redacted]

Dose Escalation Stage (Stage 1)

Dose escalation will be performed according to a modified toxicity probability interval scheme-2 (mTPI-2). HMPL-689 will be titrated using a modified Fibonacci design allowing dose increments in subsequent dose levels. The dose escalation is planned at 5 mg once daily (QD), 10 mg QD, 15 mg QD, 20 mg QD, 25 mg QD, 30 mg QD, 35 mg QD, 40 mg QD, 45 mg QD, and 50 mg QD (dose levels 1–10). The need for dose escalation beyond 50 mg QD, or other regimens, such as twice daily, will be evaluated and determined by the safety review committee (SRC) based on all available cumulative clinical safety, PK, and efficacy data.

Dose Expansion Stage (Stage 2)

The safety, tolerability, PK, and preliminary efficacy of HMPL-689 at RP2D will be further evaluated in patients with relapsed/refractory/resistant non-Hodgkin lymphoma (NHL).

Patients will receive oral doses of HMPL-689 QD at the RP2D for continuous 28-day treatment cycles until disease progression, death, intolerable toxicity, at investigator's discretion that the patient can no longer benefit from the study treatment, patient withdrawal from the study, or the end of study, whichever occurs first.

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[redacted]

4.2. DETERMINATION OF SAMPLE SIZE

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In general, the maximum sample size in the dose-escalation stage will be determined by sponsor and investigator based on the accumulated safety data and the mTPI-2 design. CCI [redacted]. Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than DLT or receive less than 75% of assigned study medication during DLT assessment window will be replaced. This may result in the actual enrollment exceeding the planned enrollment.
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STAGE 1: DOSE ESCALATION STAGE

The maximum sample size at mTPI2 for this stage will be determined by sponsor and investigator based on the accumulated safety data and mTPI-2 design. The maximum sample size under the mTPI-2 method is $k \times (d + 1)$, where k denotes the cohort size and d denotes the number of doses. The minimum cohort size in this study is 3 patients per cohort. To ensure that the highest dose (if needed) is reached per the mTPI-2 design and the availability of additional cohorts, it is estimated that approximately CCI [redacted] patients will be needed in this study.
Patients who withdraw from the study prior to completing the Dose-limiting toxicity (DLT) assessment window for reasons other than DLT or receive less than 75% of assigned study medication during DLT assessment window will be replaced. This may result in the actual enrollment exceeding the planned enrollment.

STAGE 2: DOSE EXPANSION STAGE

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Sample size justification based on Protocol Amendment 4 is outlined in Protocol Section 7.1.

4.3. SCHEDULE OF EVENTS

Schedule of events can be found in Appendix 1 of protocol amendment 5.

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[redacted]

5. PLANNED ANALYSES

There is no formal interim analysis planned for this study. However, the accrued data from any cohort may be analyzed for internal decision-making purposes.
A final analysis is planned for this study which will be performed at the end of study (defined as 18 months after the last patient has been enrolled in the study or all patients have discontinued the study treatment, whichever comes earlier in the protocol amendment 5) and after database lock.

6. ANALYSIS SETS

6.1. ALL ENROLLED SET

The all enrolled set will contain all patients who provide informed consent for this study.

6.2. FULL ANALYSIS SET (FAS)

The full analysis set (FAS) is defined as all patients who receive at least one dose of HMPL-689. The FAS will be used for analysis of safety data and efficacy endpoint PFS.

Patients will be analyzed by their actual dose initially received. If patients had their dose reduced during the study, all data will be summarized/analyzed based on the initial dose of study treatment received. However, some listings such as AE listings may give the actual dose to the patient received at the time of the AE (e.g. reduced dose, interruption etc.).

6.3. EFFICACY ANALYSIS SET (EAS)

The efficacy analysis set (EAS) is defined as all patients who receive at least one dose of HMPL-689 and have a baseline tumor assessment and at least one evaluable post-baseline assessment unless death occurs before the first post-baseline assessment. Anti-tumor efficacy endpoints: objective response rate (ORR), clinical benefit rate (CBR), time to

response (TTR), and duration of response (DoR) will be evaluated based on this analysis set.

6.4. DLT Evaluable Analysis Set (DEAS)

The DLT Evaluable Analysis Set (DEAS) is defined as all patients enrolled in the dose escalation phase of the study who are evaluable for DLT assessment. A subject is DLT evaluable if he/she meets the following criteria:

- has received at least 75% of the assigned dose of study medication during the DLT assessment window

OR

- has not completed the DLT assessment period due to a DLT

DLT assessment window is defined as the treatment period of 28 days (i.e., from Cycle 1, Day 1 [the day of the first administration of treatment] through Cycle 1, Day 28).

7. General Considerations

7.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of first non-zero administration of treatment, and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date, then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in section 7.10 Missing Data, but presented as missing in the listings.

7.2. Baseline and Change from Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken within 21 days prior to the day of first non-zero administration of treatment (including

unscheduled assessments). Bone marrow biopsy and/or aspirate are done at baseline or up to 3 months before of the Cycle 1 Day 1. In the case where the last non-missing measurement is taken on the day of first non-zero administration of treatment without time point collected, that measurement will be considered baseline. For Electrocardiogram (ECG) parameters, last assessment performed prior to or on first non-zero dose date with time point marked as "pre-dose" will be considered as baseline. Adverse Events (AEs) and medications commencing on the day of first non-zero administration of treatment will be considered post-baseline.

For quantitative measurements, change from baseline (CFB) will be calculated as:

- CFB = Assessment value at each visit – Baseline value.

Percentage CFB (% CFB) is to be calculated as:

- % CFB = (Assessment value at each visit – Baseline value)/Baseline value × 100.

7.3. LAST KNOWN ALIVE DATE

For patients in FAS who are alive at the analysis cut-off date, the last known alive date will be derived based on the last date of the following recorded dates:

- All assessment / scan / sample collection dates (e.g. laboratory evaluation, vital sign assessment, physical examination, ECG, ECOG assessment, scan dates for tumor evaluation, etc.);
- Medication dates, including study drug, concomitant medications;
- Procedure dates;
- Date of subsequent anti-tumor therapy, including subsequent chemotherapy and oncology medication, surgery/procedure and radiotherapy;
- Adverse events start and end dates, date of change of CTCAE grade, SAE started date.

For subjects who are confirmed dead in the study, the last known alive date will also be derived according to the above rules, but this date will only be used as an alternative date to impute date of death if date of death is missing.

7.4. ON TREATMENT PERIOD AND WORST POST-BASELINE

For the analysis purpose, on treatment period is defined as the period from the day of first non-zero dose of treatment to 30 days after the last dose of treatment plus protocol window of 7 days (7-day window only applies for by-visit summaries) or the initiation of new antineoplastic therapy, whichever comes earlier.

The severity of adverse events and laboratory results depends on CTCAE grade. The worst post baseline value is defined as the highest CTCAE grade during on treatment period.
The worst post-baseline abnormality is defined in the order of Abnormal, Clinically Significant (ACS) >Abnormal, Not Clinically Significant (ANCS) > Normal during the on-treatment period.
For numerical summaries, the worst post-baseline value is defined as the highest and/or the lowest numerical values.

7.5. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the worst-case value where required (e.g. shift table).
In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.
Listings will include scheduled, unscheduled, retest visits, and early discontinuation data.

7.6. SUBGROUPS

Not applicable.

7.7. WINDOWING CONVENTIONS

No analysis visit windowing will be performed for this study. The planned visit windowing is presented in Appendix 1 of protocol amendment 5.

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS Enterprise® Version 8.3 or higher version.

7.9. DATA HANDLING CONVENTIONS

Data will be summarized separately for stage 1 and 2: by dose level (Stage 1), and by malignancy type (Stage 2).
Continuous assessments will be summarized by number of patients (n), mean, standard deviation, median, minimum, and maximum. The decimal places for minimum and maximum will be the same as the max decimal places in original data. Mean and Median will keep one more decimal place than the decimal places in original data; standard deviation will keep 2 more decimal places than the decimal places in original data, but no more than 4 decimal places.
For categorical variables, descriptive statistics will include the number and percentage of patients for each category. The denominator for all percentages will be the number of patients

in that dose level or malignancy type within the population of interest, unless otherwise noted. The percentage will keep one decimal places. If the percentage is 100%, 100% will be reported; if the frequency is 0, no percentage will be reported. If needed, the 2-sided 95% confidence interval for percentage will be calculated using Clopper-Pearson method as well, and the decimal places will be the same as percentage.

7.10. MISSING DATA

In general, all available data will be included in the analyses. Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced but will be handled as 'missing' in the statistical evaluation. Partial dates may be imputed for statistical analyses for specific outcomes. In such cases, the specific imputation rules are provided below. However, as a global convention, imputed dates should not be shown in listings.

Adverse Events

If the adverse event onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication. Adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event stopped prior to the first dose of study medication or started more than 30 days after last dose of study medication or new antineoplastic therapy.

Missing or partial start dates:

- If the date has no missing year and month but the day is missing:
  1) If the year and month of first dose date are the same as the year and month of the start date, then the date of first dose will be used.
  2) Otherwise, 1st day of the month will be used.
- If the date has no missing year, but has missing month, and the year of first dose date is the same as the year of the start date, the date of first dose will be used.
- If the date has no missing year, but has missing month, and the year of first dose is not the same as the year of the start date, then January 1st will be used.
- If the start date is completely unknown, then use the date of first dose.

Missing or partial stop dates:

- If the date has no missing year and month but the day is missing, then use the last day of the month.
- If the date has no missing year, but has missing month, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date.

Note: If the imputed stop date is earlier than the start date, then the stop date is imputed with the start date. If the imputed start date is after non-imputed end date / SAE start date / date of change CTCAE grade then set start date to end date / SAE start date / date of

change CTCAE grade. For patients who died, if the imputed start/stop date is later than date of death, the imputed date will set to be date of death. If the imputed stop date is after the last known alive date, then the stop date is imputed with the last known alive date.

Concomitant Medications/Procedures

If concomitant medication starts and/or stops dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication.
Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first dose of study medication or started later than 30 days after last dose of study drug. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be prior.

Missing or partial start dates:

- If the date has no missing year and month but the day is missing, 1st day of the month will be used.
- If the date has no missing year, but has missing month, then January 1st will be used.
- If the start date is completely unknown, do not impute the start date.

Missing or partial stop dates:

- If the date has no missing year and month but the day is missing, then use the last day of the month.
- If the date has no missing year, but has missing month, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date, and assign 'ongoing' status.

Note: If the imputed stop date is earlier than the start date, then the stop date is imputed with the start date. For patients who died, if the imputed start/stop date is later than date of death, the imputed date will set to be date of death. If the imputed stop date is after the last known alive date, then the stop date is imputed with the last known alive date.

Death Date

- If year and month of death date are known but the day is unknown, day will be imputed as 1st (for example, if a patient is reported to die on Dec 2017, the death date will be imputed as 1st Dec 2017).
- If only year are known, death date will be imputed as 1st Jan of the given year.
- If the imputed death date is prior to the last known alive date, then the death date

will be imputed as last known alive date+1.

- If death date is totally missing, dates will be imputed as the last known alive date + 1.

Note: if the imputed death date is after cut-off date, then the death date will be imputed as cut-off date.

Last known alive date

- If year and month are known but the day is unknown, day will be imputed as 1st.
- If only year is known, month and day would be imputed as Jan 1st.

Last dose date

Missing or partial date of last dose date of study treatment:

- If the date is partially missing, then impute the date as the last day of given part of original last dose date. If the day is missing, imputed date will be the last day of the month of the partial last dose. If the month is missing, imputed date will be the last day of the year of the partial last dose. If the imputed date is after the date of death (if the subject died) / last known alive date (if the subject is not known to die) / EOT date / EOS date, then it will be replaced with the earliest of the above.
- If the date is completely missing, then impute the earliest of the above.

Subsequent anti-cancer therapy

Missing or partial start date of anti-cancer therapy after end of study treatment:

- If the date has no missing year and month but the day is missing. And if the date has same year and month as last dose date, then equal to last dose date+1, else 15th day of the month will be used.
- If the date has no missing year, but has missing month, and the year of last dose date is the same as the year of the start date, the date of last dose+1 will be used.
- If the date has no missing year, but has missing month, and the year of last dose is before the year of the start date, then July 1st will be used.
- If the start date is completely unknown, then use the date of last dose+1.

Oncology Diagnosis History Dates

- If year is missing, do not impute.
- if year and month are known but the day is unknown, day will be imputed as 15.
- If only year is known, month and day would be imputed as July 1st.

Note: The imputed date will be compared to inform consent date. If it is later than the inform consent date, the incomplete date will be imputed as the inform consent date.

Date of Progression/ Date of Last Tumor Assessment

- If year and month are known but the day is unknown, day will be imputed as 1st.
- If both the day and month are missing or a date is complete missing, it will be considered as missing.

Prior oncology anti-cancer Medications

Missing or partial start dates:

- If the date has no missing year and month but the day is missing, 1st day of the month will be used.
- If the date has no missing year, but has missing month, then January 1st will be used.
- If the start date is completely unknown, do not impute the start date.

Missing or partial stop dates:

- If the date has no missing year and month but the day is missing, then use the last day of the month.
- If the date has no missing year, but has missing month, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date, and assign 'ongoing' status.

Note: If the imputed stop date is earlier than the start date, then the stop date is imputed with the start date. For patients who died, if the imputed start/stop date is later than date of death, the imputed date will set to be date of death. If the imputed stop date is after the last known alive date, then the stop date is imputed with the last known alive date.

Efficacy Analyses Data

Missing efficacy response will be treated as Not Evaluable (NE) at the visit.

8. OUTPUT PRESENTATIONS

Summary results will be presented separately by Stage 1 and Stage 2.
Efficacy analysis: For Stage 1, summary will be by dose level. For Stage 2, summary will be by type of malignancies.
Analysis other than efficacy: For Stage 1, summary will be by dose level and total. For Stage 2, summary will be by type of malignancies and total.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Patient disposition, discontinuation as well as reasons for discontinuation will be presented for the all enrolled set. The number of patients who provided the informed consent for the study will be summarized, Screen failed patients and the reason for screen failure will also be summarized.
The number and percentage of patients who received, discontinued or are still on the treatment will be presented. Reasons for discontinuation from study treatment as recorded on the "End of Treatment" form will be summarized. The number and percentage of patients who have discontinued or are still on study will be presented. Reasons for discontinuation from study as recorded on "End of Study" form will be summarized. The follow up time will be also summarized with mean, median, minimum, maximum and standard deviation.
Follow up time (months) = (date of death (if the subject died) or last known alive date (if the subject is not known to die) – the first dose date + 1)/30.4375. For the interim evaluation of Stage 1 results, follow-up time (days) is defined as date of cutoff (even if patient was off treatment or died) – first dose date +1.
In addition, number and percentage of patients with <6, >=6, <12, >=12 months follow-up time will be summarized.

The number/percentage of patients included in FAS, EAS, and DEAS (stage 1 only) will be summarized based on FAS for both Stage 1 and Stage 2. A by-patient listing will include the inclusion/exclusion of patients in each analysis set.

Individual listings containing the site and subject ID, informed consent information, first and last non-zero study medication administration date, treatment discontinuation information and end of study information will be provided separately for Stage 1 and Stage 2. A separate data listing will include eligibility for study entry based on inclusion/exclusion criteria.

9.2. PROTOCOL DEVIATIONS

Protocol deviation will be collected by clinical team and entered into clinical trial management system (CTMS).
A summary table for major protocol deviations by deviation category will be presented. A subject will only be counted once within a particular deviation category even if he/she has multiple deviations under the same category.
All protocol deviation will be presented in listings including deviation category, deviation term, deviation date, severity (major/minor), actions taken, COVID-19 impact related.

COVID-19 Visit Impact to planned visit will be included in by-patient listings.

10. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be presented for the FAS.

Continuous demographic variables: age, height at baseline, weight at baseline, and body mass index at baseline will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). For all the other categorical variables, results will be presented as number and percentage of patients.
The following demographic and baseline characteristics will be reported for this study:

- Age (years) = floor (year of informed consent-year of birth)
- Age (years) category:
    - < 65
    - ≥ 65
- Gender (including childbearing potential for female patients)
- Race
- Ethnicity
- Weight at Baseline (kg)
- Height at Baseline (cm)
- BMI (kg/m2) at Baseline = weight(kg) /(height(m)*height(m))
- Tobacco Use Status
- Alcohol Use Status
- Drug Abuse Status
- Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline.
- B-symptoms (Present, Absent)
- Bone Marrow Involvement by Lymphoma

All above demographic information, cytogenetic abnormality test and bone marrow aspirate will be listed.

11. OTHER BASELINE DISEASE CHARACTERISTICS

Prior cancer diagnosis includes initial tumor type, immunohistochemistry, flow cytometry, other pathological findings.
FAS will be used to summarize baseline disease characteristics as following:

- Time since diagnosis (months): calculated as (date of first dose date – date of primary diagnosis + 1)/30.4375
- Initial Tumor Type (CLL, SLL, MCL, FL, WM/LPL, MZL, PTCL, CBCL) and sub-types for FL, MZL, and PTCL, and prior BTK inhibitor exposure for MCL only.
- Risk Groups
    - For CLL/SLL/MZL: Low, Low-intermediate, High-Intermediate, High from "Diffuse Lymphoma International Prognostic Index" CRF page
    - For FL: Low, Intermediate, High from "Follicular Lymphoma International Prognostic Index" CRF page
    - For MCL: Low, Intermediate, High from "Simplified Mantel Cell

Lymphoma International Prognostic Index (MIPI) Score" CRF page
  - For WM/LPL: Low, Intermediate, High from "International Prognostic Scoring System for Waldenstrom's Macroglobulinemia (ISSWM)" CRF page
- Rai stage (only for patients with lymphoma type CLL)
- Binet stage (only for patients with lymphoma type CLL)
- Ann Arbor Staging at study entry (for patients with lymphoma other than CLL)

All oncology diagnosis information and other baseline disease characteristics will be listed.

12. PRIOR ONCOLOGY THERAPY

Prior oncology therapy will be summarized for the FAS. Prior oncology therapies are defined as any anti-cancer therapy taken prior to initiation of study treatment.
Prior oncology therapies include prior oncology chemotherapy and oncology medication, prior oncology radiotherapies and prior oncology surgeries/procedures.

Prior oncology surgeries/procedure
Prior oncology surgeries/procedures will be coded using MedDRA Version 26.0 or higher (depends on the latest data coding). Number and percentage of patients taken prior oncology surgeries / procedure will be summarized.
All prior oncology surgeries / procedure records will be listed with system organ class (SOC) and PT in the listing.

Prior oncology radiotherapy
Radiotherapies are not considered a line of prior oncology therapy. Radiotherapies will be summarized by numbers and percentages of patients taken radiotherapies, and all radiotherapy records will be listed.

Prior oncology chemotherapy and oncology medication
Prior oncology medication therapies will also be summarized as follows:

- Number and percentage of patients with at least one prior oncology medication therapy
- Number of previous lines of therapy
- Number and percentage of patients with 1, 2, 3, and >3 previous lines of therapy
- Time since last oncology medication therapy (month) = (date of first dose – last date for the last therapy + 1)/ 30.4375
- Number and percentage of patients with Progression of Disease within 24 months

from the start of the first line of prior therapy (yes/no).

- Number and percentage of patients with any prior CD20 medication therapy
- Number and percentage of patients with any prior BTK inhibitor medication therapy

Prior oncology medications will be coded using World Health Organisation Drug Dictionary Enhanced (WHO-DDE) version MAR2023 or higher.
All prior oncology chemotherapy and oncology medication records will be listed with ATC level 2 text and preferred term (PT) in the listing.

13. MEDICAL HISTORY

Medical History information will be presented for the FAS.
All medical history from eCRF page 'Medical History' will be coded with Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 26.0 or higher.
All medical history records will be listed with system organ class (SOC) and preferred term (PT) in the listing.

14. PIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

14.1. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be presented for the FAS and will be coded using WHO-DDE version MAR2023 or higher.
Refer to Section 7.10 for handling of missing or partial dates., In the case where it is not possible to define a medication as prior or concomitant based on dates, the medication will be classified as concomitant.

- 'Prior' medications are medications which started and stopped prior to the day of the first administration.
- 'Concomitant' medications are those which:
    - Started prior to the first administration date of study medication and ended on or after the first administration date on treatment.
    - Started on or after the first administration date of study medication but no later than 30 days following last administration date on treatment.

All prior and concomitant medication records will be listed with ATC level 2 text and PT in the listing.

14.2. PRIOR AND CONCOMITANT PROCEDURES

Procedures will be presented for the FAS and will be coded using MedDRA Version 26.0 or higher.

- 'Prior' procedures are procedures which started and stopped prior to the day of the first administration.
- 'Concomitant' procedures are those which:
    - Started prior to the first administration date of study medication and ended on or after the first administration date on treatment.
    - Started on or after the first administration date of study medication but no later than 30 days following last administration date on treatment.

All prior and concomitant procedure records will be listed with system organ class (SOC) and preferred term (PT) in the listing.

14.3. SUBSEQUENT MEDICATIONS AND NON-DRUG TREATMENTS

Subsequent oncology therapy is defined as any new anti-neoplastic therapy (including chemotherapy and medication, surgery/procedure, and radiotherapy) started after last dose of study medication. Medications will be coded using WHO-DDE version MAR2023 or higher. Procedures will be coded using MedDRA Version 26.0 or higher.
Subsequent oncology therapy will be listed for the FAS with ATC2 and PT in the listing for medications and with SOC and PT in the listing for surgery and procedures.

15. STUDY MEDICATION EXPOSURE AND COMPLIANCE

Exposure to study medication will be presented for the FAS.
Date of first dose is defined as the date of first non-zero study medication administration, which will be taken from the eCRF "HMPL-689 Treatment" form.
Date of last dose is defined as the date of last non-zero study medication on or prior to withdrawal from the study or cut-off date, which will be taken from the eCRF "HMPL-689 Treatment" form. For missing or partial end dates, see imputation rule in Section 7.10.
The extent of exposure to study medication will be presented for the following summaries:

- Number of initiated cycles:
  Number of initialed cycles is the number of cycles in which the patient took any dose

of study medication.

- Total duration of exposure (months):

$$\text{Total duration of exposure (months)} = \left(\frac{\text{date of last dose - date of first dose+1}}{30.4375}\right)$$

- Number and percentage of patients with total duration of exposure
  - < 6 months
  - >=6 to < 12 months
  - >= 12 months
- Actual duration of study treatment (months):
  Actual duration of study treatment is defined as the total number of months on the study medication during the treatment phase excluding the periods of dose break or dose interruptions.

$$\text{Actual duration of study treatment (months)} = \left(\frac{\text{date of last dose - date of first dose - days with zero dose due to any cause +1}}{30.4375}\right)$$

- Cumulative dose (mg):
  Cumulative dose (mg) is defined as the sum of the total dosage that the patient actually received during an exposure period.
- Dose intensity (mg/day):

$$\text{Dose intensity (mg/day)} = \left(\frac{\textbf{Cumulative dose (mg)}}{\textbf{total duration of exposure(days)}}\right)$$

- Relative dose intensity (%):

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{dose intensity (mg/day)}}{\textbf{planned dose intensity(mg/day)}}\right) * \mathbf{100}$$

  The planned dose intensity is the initial assigned dose intensity.
  It will be summarized as a continuous variable and also categorized into groups as below:
  - < 50%
  - 50% - <70%
  - 70% - <90%
  - 90% - <110%
  - >=110%

Details of study treatment administration and exposure endpoints will be included in patient listings.

16. EFFICACY OUTCOMES

The EAS is the primary analysis set for disease response efficacy endpoints including ORR, CBR, DoR and TTR. The FAS is regarded as primary analysis set for PFS. In the evaluation of the tumor response endpoints (ORR, TTR, CBR, DoR, and PFS), the investigator-

assessed data will be utilized for tumor assessment. Unless otherwise specified, all efficacy outcomes are to be summarized by dose level in stage 1 and by the malignancy type in stage 2. Tumor assessment will be conducted every 8 weeks (±7 days) for the first 24 weeks and then every 12 weeks (±7 days) thereafter.

Tumor assessment in different types of malignancies will be evaluated according to specified guidelines/criteria:

- CLL: the modified International Workshop on CLL guideline (Hallek 2008, Cheson 2012), see Appendix 5 of protocol amendment 5.
- LPL/WM: consensus of international workshops on WM (IWWM-7 consensus) (Dimopoulos 2014), see Appendix 6 of protocol amendment 5.
- Other lymphomas: Lugano Response Criteria for Hodgkin and Non-Hodgkin Lymphoma (Cheson 2014), see Appendix 7 of protocol amendment 5.

16.1. BEST OVERALL RESPONSE (BOR)

Best overall response is defined as the best response recorded from the start of treatment until disease progression or new anti-cancer therapy, whichever comes earlier.

Best overall response is determined from the sequence of responses assessed as below:

- For CLL guideline: Complete Response (CR), CR with incomplete bone marrow recovery (CRi), Partial Response (PR), Nodular Partial Response (nPR), Partial Response with Lymphocytosis (PR-L), Stable Disease (SD), Progressive Disease (PD), Not Evaluated (NE).
- For WM guideline: Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minor Response (MR), Stable Disease (SD), Progressive Disease (PD), Not Evaluated (NE).
- For Other Lymphomas guideline: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluated (NE).

BOR will be assigned for each patient as the best response recorded from all responses recorded after study medication administration until disease progression or start of subsequent anti-tumor assessment, whichever comes earlier. For patients with multiple assessments on different dates for the same tumor assessment visit, the earliest date will be selected for PD, while the latest date will be selected for other responses.

Patients with BOR "NE" will be summarized by reason for having NE status. The following reasons will be used:

- All post-baseline assessments have overall response NE

BOR data will be listed for all patients in EAS.

16.2. OBJECTIVE RESPONSE RATE (ORR)

Objective response rate (ORR) is defined as the proportion of patients who have BOR with CR, CRi, nPR or PR for CLL patients; proportion of patients who have BOR with CR, VGPR, PR or MR for WM patients; proportion of patients who have BOR with CR or PR for patients with disease type other than CLL and WM.
The definition of neo-OR is similar to classical OR except that partial response with lymphocytosis (PR-L) is also included for CLL.
The estimated ORR, neo-OR and 95% Clopper-Pearson confidence interval (CI) will be presented by dose level for Stage 1 and by the malignancy type stage 2.
ORR data will be listed for all patients in EAS.

16.3. COMPLETE RESPONSE RATE (CR RATE)

CR rate is defined as the proportion of patients who have BOR with CR or CRi for CLL patients, and CR only for other patients.
The estimated CR rate and 95% Clopper-Pearson confidence interval (CI) will be presented by dose level for Stage 1 and by the malignancy type for stage 2.
CR rate data will be listed for all patients in EAS.

16.4. CLINICAL BENEFIT RATE (CBR)

CBR is defined as the proportion of patients who have BOR with stable disease (SD) or better.
The clinical benefit for each type of malignancy is defined as following:

- CLL: BOR with CR, CRi, nPR, PR, PR-L or SD
- WM: BOR, with CR, VGPR, PR, MR or SD
- Other types of disease: CR, PR or SD

The estimated CBR and the corresponding 95% exact CI calculated using the Clopper-Pearson method will be presented by dose level in Stage 1 and type of the malignancy for stage 2.
CBR data will be listed for all patients in EAS.

16.5. PROGRESSIVE-FREE SURVIVAL (PFS)

PFS is defined as the time (in months) from the date of first study medication to the earliest date of disease progression or death of any cause, whichever occurs first.

Progression-free survival (PFS) (months) = (<date of progression or death or censoring > - <date of first dose of study medication> + 1)/30.4375.
A patient is deemed to be censored, according to the rules specified in Table 4 below:

Table 2 Progression-Free Survival Censoring Rule

#	Situation	Date of Progression or Censoring	Outcome	Event/Censor reason
1	Death (without previously documented progressive disease [PD]) within two evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment)	Date of death	Event	Death
2	Death (without previously documented PD) after two or more consecutive missed/non-evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment)	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment)	Censored	Death after two or more consecutive missed or NE tumor assessments
3	Progression within two evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment before PD)	Date of progression	Event	Disease Progression
4	Progression after two or more consecutive missed/non-evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment before PD)	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment before PD)	Censored	Progression after two or more consecutive missed or NE tumor assessments
5	Progression after new anti-cancer treatment	Date of last evaluable tumor assessment before new anti-cancer treatment or date of first dose (if no post-baseline tumor assessment before new anti-cancer)	Censored	Progression after new anti-cancer therapy
6	No baseline tumor evaluable assessment and alive	Date of first dose	Censored	No baseline assessment
7	No post-baseline tumor evaluable assessment and alive	Date of first dose	Censored	No post-baseline assessment
8	New anti-cancer treatment started with no progression[b]/death	Date of last evaluable tumor assessment before new anti-cancer	Censored	Initiation of new anti-cancer therapy without PD/death observed

		treatment or date of first dose (if no post-baseline tumor assessment before new anti-cancer)		
9	No disease progression or death Note: use last tumor assessment before two or more consecutive missed/non-evaluable tumor assessments (if exists)	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment)	Censored	Progression free at time of analysis: the patient is known to be alive without any progression happened at the data cut-off date

Note: Only for tumor assessments and death date before cutoff date.
[a] time period that identifies two consecutive missed/non-evaluable tumor assessments is calculated as 2*(the planned duration between assessments + protocol allowed visit window) from the last evaluable tumor assessment or (2*the planned duration between assessments + 1*protocol allowed visit window) from date of first dose (if no post-baseline evaluable tumor assessment).
According to protocol, tumor assessment will be conducted every 8 weeks for the first 24 weeks and every 12 weeks thereafter (±7 days). Given the schedules visit assessment scheme, the definition of two missed consecutive tumor assessment visit may vary, please refer to following rule:

- If the last evaluable tumor assessment before PD/death is on or before Day 105 (week 15, which is 8 weeks before week 24, and allowing for 7 days for early visit, hence 7*16 weeks - 7 days for a late visit =Day 105), then two consecutive assessments equates to 126 days since last evaluable tumor assessment, allowing for early and late visits (2*8 weeks + 7 days for an early assessment + 7 days for a late assessment), or 119 days since date of first dose, allowing for late visit (2*8 weeks + 7 days for a late assessment).
- If the two missed assessments occur over the period when the scheduled frequency of tumor assessments change from 8-weekly to 12-weekly, which means last evaluable tumor assessment is from week 16 to 23 (Day 106 to Day 161), then two consecutive assessments equates to 154 days (7*8 weeks + 7*12 weeks + 7 days for an early assessment + 7 days for a late assessment) since last evaluable tumor assessment.
- From Day 162 (week 24) onwards (when the scheduling changes to 12-weekly assessments), two missing consecutive assessments equates to 182 days (2*12 weeks + 7 days for an early assessment + 7 days for a late assessment) since last evaluable tumor assessment.

[b] for patients who receive new anti-cancer therapy, the following rules will apply:
If the start date of new anti-cancer therapy is partial or missing, the imputation rules refer to section 7.10.
If an assessment occurs on the same day as the start of new anti-cancer therapy, the assessment will be used as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy).

The median and quartiles for PFS and the PFS rates at 6 months, 12 months, together with their two-sided 95% confidence intervals will be estimated for each dose level (Stage 1) and malignancy type (Stage2) using the Kaplan-Meier method. The 95% CI for the median will be calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982).
Kaplan-Meier curves will be plotted. In case the number of responses in each group is very small, PFS may be listed only.

PFS follow-up time will be summarized by reversed Kaplan-Meier method (i.e. using different censoring rule which reverses censoring indicator of PFS, i.e. patients who progressed or died in PFS analysis will be censored at the date of progression or death, patients who are censored in PFS analysis will be assigned indicator of "event" with the same duration for PFS) to calculate median, first and third quartiles and 95% CIs.

Frequency and percentage for each type of event (PD or death) and censoring reasons will be presented as categories.
The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing for FAS.

16.6. DURATION OF RESPONSE (DOR)

Duration of response (DoR): defined as the time from when the first response (CR, CRi, PR, nPR, VGPR, PR-L, and MR) was achieved until the earlier of the first documentation of definitive disease progression or death from any cause, whichever is earlier. If patients do not have disease progression or death, they will be censored following the same rules as for PFS. Only patients with response of CR, CRi, PR, nPR, VGPR, PR-L, or MR will be included in the analysis for DoR.
DoR (months) = (<date of first documentation of definitive PD or death from any cause or censoring > - <date of first response> + 1)/30.4375.
Median and quartiles for DoR, and the DoR rates at 6 months, 12 months, along with the two-sided 95% CI will be estimated and Kaplan-Meier curve will be plotted by dose level in stage 1 and by the malignancy type in stage 2. The 95% CI for the median will be calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982).
DoR data will be listed for all patients in EAS.

16.7. TIME TO RESPONSE (TTR)

TTR is defined as the time from the first dose of study treatment to the first occurrence of CR, CRi, PR, nPR, VGPR, PR-L, or MR. Only patient with response of CR, Cri, PR, nPR, VGPR, PR-L, or MR will be included in the analysis for TTR.
TTR = (<date of first response> - <date of first dose of study medication> + 1)/30.4375.
TTR will be summarized by descriptive statistics by dose level in stage 1 and by the malignancy type in stage 2.
TTR data will be listed for all patients in EAS.

16.8. TUMOR BURDEN

Tumor burden is defined as the sum of the product of diameters of all target measurable lesions at each tumor assessment visit.

The best percent change from baseline in tumor burden is calculated as:

- (The minimum tumor burden among post-baseline assessments – Baseline tumor burden value)/Baseline tumor burden value × 100

Tumor burden will be missing for that assessment visit if there is a missing value of the product of diameters. Thereof a patient will be considered not evaluable for the measure of the best percent change from baseline in tumor burden for that visit.

Best percent change from baseline in tumor burden will be summarized by descriptive statistics. A waterfall plot of the best percent change from baseline in tumor burden will be presented for EAS, BOR will be labeled in the plot. Patients without any baseline or evaluable post-baseline assessments will be completely excluded from the plots. Patients without any target lesions at baseline will be excluded as well.

Different color will be presented to differentiate various dose levels (for stage 1) and the different type of malignancy in stage 2.

A listing with the tumor assessments at baseline and each tumor assessment visit will be presented, including each component for tumor assessment.
A swimmer plot of duration of treatment will be presented from date of first dose until date of last dose. Treatment reduction and interruption will be shown in the exposure box for each patient. Tumor responses for each tumor assessment will also be labeled in the plot.

17. SAFETY OUTCOMES

All summary results for safety outcomes will be based on the FAS, except DLTs summaries which are based on the DEAS.
Adverse Events (AEs) will be coded using MedDRA version 26.0 or higher. AE and laboratory test results severity will be performed with the National Cancer Institute Common Terminology criteria for adverse events (NCI CTCAE) V5.0.

17.1. DOSE LIMITING TOXICITIES (DLTS)

DLT is defined as the occurrence of any of the following treatment emergent adverse events (TEAE) during the DLT assessment window (Cycle 1, Day 1 through Cycle 1, Day 28), unless clearly unrelated to study medication:

a. Nonhematologic toxicity: All nonhematologic TEAEs of Grade 3 or greater with the

exception of:
   i. Grade 3 nausea or vomiting that can be controlled by supportive therapy
b. Hematologic toxicity:
   i. Grade 4 neutropenia lasting for more than 5 days
   ii. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding event or requiring platelet transfusion
   iii. Grade ≥3 febrile neutropenia (defined as ANC <1000/mm3 with a single temperature of >38.3ºC [101ºF] or a sustained temperature of ≥38ºC [100.4ºF] for more than 1 hour)
   iv. Grade 4 anemia not explained by underlying disease
c. Any TEAE requiring a dose delay of ≥15 days
d. Any case of Hy's Law (defined as the finding of an elevated ALT or AST in combination with either an elevated total bilirubin (≥2 × ULN)) collected as Adverse Event of Special Interest.

For all patients in Stage 1, DLTs will be assessed during a DLT assessment window of 28 days (i.e. from Cycle 1, Day 1 [the day of first administration of treatment] through Cycle 1, Day 28). DLT is collected in the "Dose-Limiting Toxicity Assessment" CRF page.

DLT will be coded using MedDRA Version 26.0 or higher. The number and percentage of patients with DLTs will be based on the number of patients in the DEAS by SOC, PT and CTCAE grade. SOC/PT will be sorted in descending frequency of the total number of patients, SOC/PT will be presented alphabetically for SOC/PT of the same frequency. By-patient listing of DLTs will be presented with SOC, PT and CTCAE grade in the listing.

17.2. ADVERSE EVENTS

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the first dose of study medication and no later than 30 days after the date of last study treatment administration or start of a new treatment of anti-neoplasm therapy, whichever is earlier. An exception is that study medication related SAE collected later than 30 days after the last treatment date or start of a new treatment of anti-neoplasm therapy will be treated as TEAEs.

Refer to Section 7.10 for handling of partial dates for AEs. In the case where it is not possible to classify an AE as treatment-emergent or not, the AE will be classified as treatment-emergent.

All AEs will be listed, and only TEAE will be summarized.

The missing severity will be classified as grade 3. Relationship, as indicated by the Investigator, is classified as "Not related", "Related". TEAEs with a missing relationship to study medication will be regarded as "related" to study medication.

TEAE OVERVIEW

An overall summary of TEAEs will include the number of patients with:

- Any TEAE
- Any TEAEs by maximum CTCAE grade
- Any TEAE of CTCAE Grade 3 or higher
- Any TEAE Leading to Dose Modification
    - Any TEAE Leading to Dose Reduction
    - Any TEAE Leading to Drug Interruption
- Any TEAE Leading to Drug Discontinuation
- Any TEAE Leading to Death
- Any Treatment Related TEAE
- Any Treatment Related TEAE of CTCAE Grade 3 or higher
- Any Treatment Related TEAE Leading to Dose Modification
    - Any Treatment Related TEAE Leading to Dose Reduction
    - Any Treatment Related TEAE Leading to Drug Interruption
- Any Treatment Related TEAE Leading to Drug Discontinuation
- Any Treatment Related TEAE Leading to Death
- Any Serious TEAE
- Any Treatment Related Serious TEAE
- Any Special Interest TEAE (AESI)
- Any Treatment Related AESI

TEAE SUMMARY

All TEAE will be summarized (the number and percent of patients) by SOC, PT and maximum CTCAE grade (All Grade, Grade ⩾3, Grade 1/2).

The following categories will be summarized (the number and percent of patients) by PT and maximum CTCAE grade (All Grade, Grade ⩾3, Grade 1/2).

	Summary scope
TEAE	– Any TEAE – TEAEs with CTCAE grade 3 or higher (maximum CTCAE grade by Grade 5, Grade 4, Grade 3) – TEAEs leading to dose modification o TEAEs leading to dose interruption o TEAEs leading to dose reduction – TEAEs leading to discontinuation of study drug – TEAEs leading to death (by PT only)

	Summary scope
Treatment-related TEAE	– Any treatment-related TEAE – Treatment-related TEAEs with CTCAE grade 3 or higher (maximum CTCAE grade by Grade 5, Grade 4, Grade 3) – Treatment-related TEAEs leading to death (by PT only)
Serious TEAE	– All serious TEAE – Treatment-related serious TEAEs

If a subject experienced the same adverse event (as identified by MedDRA preferred term) more than once during the study, the worst occurrence (e.g. worst grade) will be counted. Similarly, if a subject experienced more than one occurrence of the same SOC/PT, the worst occurrence (e.g. worst grade) will be counted within a particular SOC/PT. When summarizing AE by CTCAE grade, if a subject experienced more than one occurrence of the same SOC/PT, the worst severity grade will be counted. Each summary will be ordered by descending order of incidence of SOC and PT within each SOC. If the frequencies of SOC/PT tie, an alphabetic order of SOC/PT will be applied

- Serious adverse events (SAEs) are those adverse events recorded as "Serious" on the "Adverse Events" page of the (e)CRF.
- AEs leading to study medication reduction will be identified as those AEs with a response of "Dose reduced" to the item "Action taken with the study treatment" in the eCRF page of "Adverse Events".
- AEs leading to study medication interruption will be identified as those records with a response of "Drug interrupted" to the item "Action taken with the study treatment" in the eCRF page of "Adverse Events".
- AEs leading to discontinuation of study medication are those AEs with "Drug permanently discontinued" dose action from the eCRF page of "Adverse Events".
- AEs leading to Death are those events which are recorded as "Fatal" in Outcome question/Serious AE related question or Grade 5 in CTCAE grading system on the "Adverse Events" page of the (e)CRF.

AESI SUMMARY

AEs of special interest (AESI) are listed in the below table, and will be identified by MedDRA Query (SMQ):

AESI Category	Search terms	SMQ Code
Hepatic function abnormal	MedDRA SMQ "Drug related hepatic disorders - comprehensive search [exclude tumors]" (narrow)	20000006 (exclude: 20000011, 20000012)

Infective pneumonia	MedDRA SMQ "Infective pneumonia" (narrow)	20000231
Colitis or diarrhoea	MedDRA SMQ "Noninfectious diarrhoea" (narrow+broad)	20000218
Interstitial lung disease	MedDRA SMQ "Interstitial lung disease" (narrow)	20000042
Severe cutaneous adverse reactions	MedDRA SMQ "Severe cutaneous adverse reaction" (narrow)	20000020

All AESIs will be summarized in frequency and percent by AESI category, PT and maximum CTCAE grade (All Grade, Grade ⩾3, Grade 1/2). The followings will also be summarized for each AESI category:

- AESI
- Treatment Related AESI
- AESI of CTCAE Grade 3 or higher
- AESI meeting SAE criteria
- AESI leading to dose modification
- AESI leading to dose reduction
- AESI leading to dose interruption
- AESI leading to dose discontinuation
- AESI leading to death

Moreover, time to AESI onset (days), AESI duration (days) and AESI outcome (the number and percent of patients) will be summarized descriptively.
Time to AESI onset is defined as the time interval from the date of first dose of study drug to the earliest onset date among all AESIs. That is, if a subject has multiple AESI occurrences, the earliest AESI onset date will be used as the onset date to calculate time to onset of AESI.
AESI duration (days) will only be calculated for ended AESI as (AE end date-AE start date+1).

All AE will be listed, including AE term, start date, end date, severity, whether the AE is DLT, change of CTCAE grade, whether the AE is SAE, classification of SAE (if SAE), whether the AE is AESI, relationship to study drug, action taken, outcome will be presented in subject data listings. If the AE is ongoing at the data cut-off date, it will be reported as 'Ongoing' in the listing.
In addition, separate listings of all SAEs, AESIs, AEs leading to death and AEs leading to discontinuation of study drug will be provided.

17.3. DEATHS

The information recorded in CRF "Death Details" page will be presented in the listing, and the on-treatment death (defined as death during the date of first dose to 30 days after the last dose of study drug or prior to the start of a new anti-cancer therapy, whichever comes first) will be flagged.

17.4. LABORATORY EVALUATIONS

Laboratory evaluations will be performed in the site laboratory. Laboratory evaluations to be included in the outputs are included in the protocol, section 5.7.10, including hematology, chemistry panel, serum amylase and lipase, fasting lipid profile, coagulation, thyroid hormones, serum β-2 microglobulin, viral serology, urinalysis, leukocyte immunophenotyping, pregnancy testing, serum immunoglobulins assessment from the study site's local laboratory. All laboratory results (including pregnancy test results) will be included in listings.
Laboratory results will be converted to International Standard Units (SI Units), and all the analysis and presentation will be based on SI units.

The incidence of patients with the following elevations abnormal liver function tests (Hy's Law) at post-baseline will also be summarized:

- ALT or AST >3 x ULN and <= 5 x ULN (based on the worst post-baseline case)
- ALT or AST > 5 x ULN (based on the worst post-baseline case)
- Total bilirubin >= 2 x ULN (based on the worst post-baseline case)
- (ALT or AST >3 x ULN) and total bilirubin >= 2 x ULN [defined as total bilirubin increase by >= 2 x ULN within 14 days after ALT or AST increase by > 3 x ULN]
- Hy's law: (AST or ALT >3 x ULN) and total bilirubin >= 2 x ULN and ALP < 2 x ULN [defined as total bilirubin increase by >= 2 x ULN and ALP increase <2 x ULN within 14 days after ALT or AST increase by > 3 x ULN]

All laboratory evaluation records and abnormal liver function will be listed.

17.5. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.
The following ECG parameters will be reported:

- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) = QT interval/cube root of RR interval $\frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant
    - Abnormal, Clinically Significant

All ECG evaluation data will be listed

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17.6. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (ºC)

All vital sign data will be listed.

17.7. PHYSICAL EXAMINATION

All physical examination data will be listed.

17.8. ECOG PERFORMACE STATUS

ECOG Performance Status Grade List

Grade	Activity Level
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Death

All ECOG performance status data will be listed.

17.9. ECHOCARDIOGRAM/MUGA

All Echocardiogram/MUGA data will be listed.

18. REFERENCES

EMA. (n.d.). *Guideline on Missing Data in Confirmatory Clinical Trials*. Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

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