Janssen Research & Development

Statistical Analysis Plan

A Phase 1/2a Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the Combination of Ibrutinib with Nivolumab in Subjects with Hematologic Malignancies

Protocol PCI-32765LYM1002; Phase 1/2a

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

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ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
DLBCL	Diffuse large B-cell lymphoma
CI	confidence interval
CR(s)	complete response(s)
CRI(s)	complete response(s) with incomplete marrow recovery
CRF	case report form
CSR	clinical study report
DOR	duration of response
DOSD	duration of stable disease
ECOG	Eastern Cooperative Oncology Group
FL	follicular lymphoma
HCV	hepatitis C virus
Ig	immunoglobulin
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	lactic acid dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NPR	Nodular partial response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR(s)	partial response(s)
PRL(s)	partial response(s) with lymphocytosis
PT	Preferred Term
RP2D	recommended phase 2 dose
SAP	statistical analysis plan
SCT	stem cell transplant
SD	stable disease
SLL	Small lymphocyte lymphoma
SOC	System Organ Class
TB	total bilirubin
transformed DLBCL	FL transformed to DLBCL
ULN	Upper Limit of Normal
WBC	white blood cell (count)
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This is a Phase 1/2a Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the Combination of Ibrutinib with Nivolumab in Subjects with Hematologic Malignancies. There are two parts of this study. Part A (Dose Optimization Cohorts) is to determine whether ibrutinib and nivolumab can be safely combined and to establish the recommended Phase 2 dose (RP2D) for this combination in subjects with hematological disorders. Part B (Expansion Cohorts) is to determine the preliminary activity of the ibrutinib/nivolumab combination regimen in subjects with CLL/SLL with del 17p or 11q (Cohort B1), FL (Cohort B2), DLBCL (Cohort B3), and Richter syndrome (Cohort B4) in comparison to historical results.

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and data handling rules, and statistical approaches for the evaluation of safety, preliminary efficacy activities, and pharmacokinetics. Biomarker analysis will be included and described in this document.

1.1. Trial Objectives

The preliminary clinical activity of ibrutinib in combination with nivolumab in each disease type of part A and B in the all-treated population will be explored via the following endpoints unless otherwise stated: objective response rate [PR(+L) or better], progression-Free Survival (PFS) and overall survival (OS), duration of response (DOR) and duration of stable disease (DOSD) will be evaluated if there are sufficient data for responders for each disease-specific cohort A1, A2, B1, B2, B3 and B4 on the all-treated population. Furthermore, objective response rate [PR(+L) or better] will also be explored on the response-evaluable population, if deemed necessary. In addition, the safety profile of the ibrutinib and nivolumab combination regimen will be evaluated and the pharmacokinetic profile of ibrutinib and nivolumab compared with existing single-agent treatment data; and the potential relationships between ibrutinib and nivolumab metrics of exposure with relevant clinical or biomarker information will be characterized and explored.

1.2. Trial Design

This is an open-label Phase 1/2a study, which consists of Part A (Dose Optimization Cohorts A1 and A2) and Part B (Expansion Cohorts B1, B2, B3 and B4). In the context of this study, a treatment ‘cycle’ is defined as a course of treatment of 14 days starting with the intravenous administration of nivolumab on Day 1 of each cycle along with once daily oral intake of ibrutinib on all days.

It is anticipated that approximately 158 subjects for both Parts A and B would be enrolled.

Part B (Dose Expansion Cohorts) will be open for enrollment after the RP2D is determined in Part A. In Part B, further assessment of the RP2D will be explored in 4 subject populations to further evaluate the safety and clinical activity of ibrutinib in combination with nivolumab. During the expansion period, subjects with CLL/SLL with del 17p or 11q (Cohort B1), FL (Cohort B2), DLBCL including FL transformed into DLBCL (transformed DLBCL) (Cohort B3), and Richter syndrome (Cohort B4) will be enrolled. Approximately 35 subjects will be

enrolled in each of the expansion cohorts. The subjects will be treated at the RP2D level selected to further assess the safety, pharmacokinetics, pharmacodynamics, pharmacogenomics, and activity of the combination.

The median duration of study therapy is expected to be approximately from 2 (DLBCL) to 15 (CLL) months.

The End-of-Treatment Visit will occur within 30 days after the last dose of ibrutinib or nivolumab, whichever treatment occurred last.

During the Follow-up Period, long-term safety, survival status, disease progression, subsequent aniticancer therapy, and occurrence of other primary malignancy data will be collected. During the Follow-up Period, subjects should be followed for safety up to 30 days after the last dose of ibrutinib or 100 days after the last nivolumab infusion, whichever is later. The safety includes adverse event reporting and laboratory assessments (at the first follow up). Thereafter Follow-up visits will be completed approximately every 3 months until death or the end of study. Subjects who have developed treatment-related Grade 3 or higher toxicity at the end of treatment will be assessed until recovery to Grade ≤1 or baseline, deemed irreversible, or until end of study. Adverse events leading to discontinuation will be followed up until resolution or return to baseline, or end of study, whichever occur first.

The primary analysis of the study will be performed 6 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. After the cut off for primary analysis, subjects who are receiving study treatment can continue treatment per protocol until progression, unacceptable toxicity, withdrawal of consent, or other reason as listed in protocol Section 11.2. End of study will be defined as the time when all subjects have completed the End-of-Treatment Visit and have been followed for safety up to 100 days post nivolumab as the last study assessment.

1.3. Statistical Hypotheses for Trial Objectives

This study will evaluate and describe whether ibrutinib combined with nivolumab can result in an overall response rate of more than 20% in each cohort of part B (i.e., dose expansion, cohorts B1, B2, B3 and B4), respectively.

1.4. Sample Size Justification

The sample size is calculated based on the following assumptions:

- The overall response rate under null hypothesis is 20%
- The overall response rate under alternative hypothesis is at least 38%
- The probability to mistakenly rejecting the null hypothesis when it is actually true is 0.1 (one-sided).
- The probability to correctly rejecting null hypothesis when alternative hypothesis is true is at least 0.8

Under the above assumptions, the study will enroll approximately 35 subjects to get at least 32 response evaluable subjects in each cohort of Part B (Cohorts B1, B2, B3, and B4).

2. GENERAL ANALYSIS DEFINITIONS

2.1. Analysis Cohorts

Disease type cohort is defined as: cohort of patients grouped by disease type of CLL, SLL, DLBCL, transformed DLBCL, (i.e., FL transformed to DLBCL), DLBCL overall (include both DLBCL and transformed DLBCL) Richter Syndrome from both Part A and B, unless otherwise stated. Study cohort is referring to cohorts A1, A2, B1, B2, B3 and B4.

2.2. Visit Windows

Visit window will be based on phases and cycles:

(For the purposes of this study, 'study drug' or 'study therapy' or "study treatment" refers to both ibrutinib and/or nivolumab).

Screening: Up to 28 days before the start of any study treatment.

Treatment: Between the date of first administration of study therapy and the date of the last dose of study drug. The treatment stage will be subdivided by cycles. Each cycle is 14 days, starting from the first dose of study drug. The end date of the last cycle is the date of the last dose of study drug received during the study.

End of treatment: within 30 days after the last dose of ibrutinib or 100 days after the last nivolumab. The assessments performed during the 'End of treatment visit' will be included in this End of treatment phase.

Follow-up: After the end of treatment till the last assessment for the last subject in the study (e.g. the last follow-up visit or death).

Baseline assessment is defined as the last non-missing results on or before the first dose of study therapy.

1. Cycle-based analysis may be performed for safety parameters during the treatment up to date of last dose of ibrutinib + 30 days, and last dose of nivolumab +100 days. For the analysis of laboratory measurement by cycle, the mean values within each cycle will be used. For the analysis of laboratory grade by cycle, the worst grade within each cycle will be used.

Assessments will be presented chronologically by cycle day or study day, which are defined as the follows:

Day 1 = date of first dose of study drug / Cycle 1 day -7 (subjects with run-in)

Study Day (if on or after date of first dose) = assessment date – date of first dose +1

Study Day (if before date of first dose) = assessment date – date of first dose

Cycle Day = assessment date – date of first dose for the cycle +1

2.3. Pooling Algorithm for Analysis Centers

The data from all investigative sites will be pooled for all analyses.

2.4. Analysis Sets

2.4.1. Efficacy Analysis Set(s)

The all-treated population is defined as all subjects who have received at least 1 dose of study drugs (either ibrutinib or nivolumab).

The response-evaluable population is defined as all subjects who receive at least 1 dose of both study drugs (ibrutinib and nivolumab), and have a pretreatment, and at least 1 posttreatment disease assessment; unless no post-baseline scan was performed due to AE possibly related to treatment or clinical progression or death.

ORR, DOR, DOSD, PFS and OS will be analyzed using the all-treated population. In addition, ORR will also be analyzed based on response-evaluable, if deemed necessary.

DOR will be analyzed for subjects who achieve a partial response [PR (+L)] or better. DOSD will be analyzed for subjects who achieve a stable disease (SD) or better.

2.4.2. Safety Analysis Set

The safety population is defined as all subjects who receive at least 1 dose of study drug, which is same definition as the all-treated population.

2.4.3. Pharmacokinetics/Pharmacodynamic (PK/PD) Analysis Set

This population consists of all subjects who receive at least 1 dose of study drug (either ibrutinib or nivolumab) and have at least 1 posttreatment sample collected during treatment to determine the concentration or pharmacodynamic biomarker response.

2.5. Definition of Subgroups

Exploratory subgroup analyses will be performed for the primary efficacy endpoint.

- Age (<65 vs. ≥65 years)
- Sex (male vs. female)
- Race (Caucasian vs. Other)
- Prior lines of therapy (1 vs 2 to 4 vs >4)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 vs 2)
- Region (United States vs. Non-United States)

- SLL vs Non-SLL
- Transformed DLBCL vs Non-transformed DLBCL

2.6. Imputation of Missing Dates

In general, missing date of initial diagnosis, date of death and start and end dates of AE, prior, concomitant and subsequent therapies will be imputed according to the following rules:

- General rules
  - If date is completely missing or year is missing, no imputation will be made.
  - If only year is present but month and day are missing, then June 30th will be used.
  - If only day is missing but year and month are available, then the 15th of the month will be used
- Start and end dates rules
  - Start date will be imputed before end date
  - If end date is not missing (i.e., not imputed) and before the imputed start date, then end date will be used
  - If end month and year are not missing and before imputed start month and year, then end month and year will be used
  - If imputed end date is before start date, then start date will be used

However, the above imputation will be modified by the following rules sequentially:

- For death: if the imputed date is before the last date that the subject is known to be alive, the latter date + 1 day will be used.
- If any imputed date is after date of death, then date of death will be used
- For initial diagnosis and prior therapies: if imputed date is on or after the first dose date, then first dose date - 1 will be used.
- For AE and concomitant medications: The imputed start date will be adjusted sequentially using the following steps
  - If it is in the same month and year but before the first dose date, then the first dose date will be used, or if it is in the same month and year but after the last dose date + 30 days, then the last dose date + 30 days will be used
  - If the end date is not missing and the imputed start date is after the end date, then the end date will be used.

- If the imputed start date and is after date of death, then date of death will be used.
- If it is in the same month and year but after the 1st subsequent systemic therapy start date, then the 1st subsequent therapy start date will be used.
- For subsequent therapies: if imputed date is before the treatment discontinuation date, then the treatment discontinuation date will be used.

2.7. Other General Definitions

Year and Month

1 year = 365.25 days and 1 month = 30.4375 days.

Age

Use Age (year) collected in the case report form (CRF), which is the number of integer years from the date of birth to the date of informed consent.

Date of overall response for each time point

Date of assessment at that time point. When different assessments for the time point are performed on different dates, the date of overall response is the date of the last assessment performed when the responses PR(+L) or better [except for biopsies - biopsies of tumor or suspected tumors (such as lymph nodes/nodal masses) or extranodal masses (such as GI biopsy, skin lesions, etc.), cytology assessments], or the date of earliest assessment showing progression when the response is PD or relapse from CR.

Date of response

Date of first observed response [PR(+L) or better]. For CLL patients, time to response is calculated from onset of PRL.

Date of best response

Date of first observed best response [PR(+L) or better]. For instance, for subjects who achieved PR followed by CR, PR will be the initial response and CR will be the best response (the date of evaluation with first time CR is reported is the date of best response). Use the ranking below to choose the best response. The response corresponds to the lowest rank of number is the best response:

Rank	Response
1	CR
2	CRI
3	PR
4	NPR
5	PR WITH LYMPH (PRL)

6 SD or no response
7 PD
8 NE
10 UNK
11 (missing)

Date of progression

Date of first observed progression.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

All demographics and baseline characteristic variables will be summarized for the all-treated population by disease type and study cohorts.

No formal statistical hypothesis testing is planned.

- Demographic and baseline characteristics data, including age (continuous and grouped as <65, or ≥65 years), sex, race, ethnicity, weight, height, and ECOG performance status will be summarized.

- Disease characteristics at baseline including time from initial diagnosis to first dose, lymphoma-related symptoms, lactic acid dehydrogenase (LDH), number of lines of prior therapies (continuous and grouped as 1 and 2 to 4 and >4) and lymphocyte count (at baseline).

- Chemistry: creatinine, AST, ALT, total bilirubin, lipase and amylase

- Hematology: hemoglobin, white blood cell, absolute neutrophils, absolute lymphocyte count, and platelet count

- Beta2-microglobulin, serum immunoglobulin levels (IgG, IgM, IgA). For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the number and percentage of subjects in each category will be summarized.

3.2. Disposition Information

Disposition will be summarized for the all-treated population by disease type and study cohorts, including the number and percentage of subjects who are treated and discontinued treatment as well as their reason for discontinuation. Similarly, number of subjects undergoing and discontinuing the study as well as their reasons for study discontinuation will be summarized.

3.3. Medical History

Abnormal medical history findings reported by the investigator will be summarized by body system.

3.4. Extent of Exposure

Extent of exposure for ibrutinib will be summarized for the safety population by disease type and study cohorts. Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for total number of cycles, treatment duration (the interval between date of first dose and date of last dose), and ibrutinib dosing information including total dose received (the sum of administered doses), dose intensity (the ratio of total dose and treatment duration).

Dose reduction for ibrutinib is defined as administered planned lower dose level. There is a one applicable dose level reduction for CLL/SLL cohort: 280 mg/day (level 1 reduction). There are two applicable dose level reductions in FL, DLBCL or Richter syndrome disease cohorts: 420 mg/day (level 1 reduction) or 280 mg/day (level 2 reduction). Dose reduction information will be summarized for the number of subjects with any dose reduction (at least 1 reported dose reduction), as well as the frequency and reason of dose reduction. Number and percentage of subjects with cycle delays will also be presented.

Dose interruption for ibrutinib is defined as missing/skipped dose for $\geq$ 7 day. The consecutive days of dose interruption are considered as 1 dose interruption. The number and percentage of subjects with dose reduction and dose interruption will be summarized. In addition, subjects with dose modifications (i.e., reductions or interruptions) and reasons for dose modifications will be summarized.

Extent of exposure for nivolumab will be summarized for the safety population by disease type and study cohorts. Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for total number of infusion, infusion duration (the interval between the start time of infusion and the end time of infusion), infusion rate interruption duration (the interval between the start time of infusion interruption and the end time of infusion interruption), and nivolumab dosing information including, total dose administered/received (the sum of actual dose administered), total number of infusions interrupted, total number of infusions skipped, total number of infusions discontinued and total number of infusion rate reductions, interval between 2 consecutive infusions of nivolumab which is defined as end date of prior cycle to first day of following cycle.

Dose modification is defined as at least 1 dose skipped or events occurred during infusion. The frequency and reason of dose skipped or events occurred during infusion will be summarized.

3.5. Protocol Deviations

Subjects with eligibility and major protocol deviations will be summarized and listed, as appropriate. Protocol deviations will be based on clinical review for the following aspects, but

not limited to: (1) eligibility, (2) treatment compliance, (3) patient safety, and (4) efficacy assessment deviation. Protocol deviations will be closely monitored during the execution of the study and the final set of protocol deviation criteria will be finalized before database lock.

3.6. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by the World Health Organization Drug Dictionary (WHO-DD) therapeutic class, pharmacological class, and preferred term.

4. EFFICACY

The primary population for the primary efficacy endpoint, ORR, is the all-treated. Sensitivity analysis will be performed on the response-evaluable population, if deemed necessary. Unless otherwise specified efficacy analyses will be based on the all-treated population.

4.1. Analysis Specifications

4.1.1. Level of Significance

If deemed applicable, all tests will be 1-sided. The primary efficacy endpoint will be tested at the overall significance level of 0.025. For result presentation purpose, a 2-sided 95% confidence interval will be used.

4.1.2. Data Handling Rules

Unless otherwise specified, missing values will not be imputed.

4.1.3. General Analysis Considerations

For this study and its CSR, analyses of disease response and disease progression are based on investigator assessments. These assessments are based on IWCLL [International Workshop on Chronic Lymphocytic Leukemia (Hallek 2008)] for CLL patients and the Lugano Classification by Cheson (2014) for SLL, FL, DLBCL and Richter syndrome and using data collected at the clinical cutoff. Detailed criteria for response category can be found in Section 10.1 of the protocol. All the additional data collected after the clinical cutoff will be summarized in the CSR addendum.

4.2. Primary Efficacy Endpoint(s)

4.2.1. Definition

The primary endpoint is ORR, defined as the proportion of subjects who achieve partial response or better [PR(+L) or better], as assessed by the investigators at or prior to initiation of subsequent anti-cancer therapy. The primary efficacy analysis of ORR will be conducted at performed 6 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. The analysis will be based on the all-treated population.

4.2.2. Analysis Methods

The response rate and its 95% exact (Clopper-Pearson) CI will be calculated. Subgroup analysis will be provided. Sensitivity analysis will be performed using the response-evaluable population.

A listing of tumor response by assessment visit will be provided.

4.3. Exploratory Secondary Endpoints

4.3.1. Duration of Response

Definition

Duration of response is defined as the interval between the date of initial documentation of a response [PR(+L) or better] and the date of first documented evidence of PD (or relapse for subjects who experience CR during the study) or death, whichever occurs first. Subjects who are progression-free and alive, or have unknown status will be censored at the last adequate disease assessment.

Analysis method

Duration of response will be analyzed for subjects with PR(+L) or better. The distribution of duration of response will be estimated using the Kaplan-Meier method. The primary analysis will be based on response data by investigator assessment.

4.3.2. Duration of Stable Disease or Better

Definition

Duration of stable disease or better is measured from the start of the treatment until the criteria for progression are met.

Analysis method

Duration of SD or better will be analyzed using descriptive summary statistics. Subjects whose progression criteria are not met at clinical cut-off will be censored at the last adequate disease assessment.

4.3.3. Progression-free Survival and Overall Survival

Definition

PFS is defined as the interval between the date of first dose of study drug and the date of first documented evidence of PD (or relapse for subjects who experience CR during the study) or

death, whichever comes first. Subjects who are progression-free and alive, or have unknown status will be censored at the last adequate disease assessment.

OS is defined as the interval between the date of the first dose of study drug and the date of the subject's death from any cause. If the subject is alive at the time of the cut-off, it will be censored at the last known alive date (the last date among visit date, AE start and end dates, treatment date, disease assessment date, and survival follow up date, and if available, survival sweep date, etc.).

Analysis method

Similar analyses will be applied to OS and PFS as those used for duration of response. The distribution of PFS and OS will be estimated using the Kaplan-Meier method.

The primary analysis of PFS will be based on assessments by investigator. The reason of censoring will be summarized for OS and PFS. The median follow-up duration will be provided. Follow-up duration is defined as OS with reversed censoring, i.e., subject who died will be censored. The Kaplan-Meier method will be used to estimate the median follow-up.

4.3.4. Resolution of Lymphoma-related symptoms

Frequency and percentage of subjects with lymphoma-related symptoms will be summarized by cycle. All-treated population will be used.

For subjects who have reported symptoms at baseline and had at least one time point of assessment post baseline (before the start of subsequent therapy), the following summaries will be provided for the resolution of symptoms:

- Frequency and percentage of subjects who have no symptoms reported at least one post baseline time point (before the start of subsequent therapy)

    - Duration of resolution is defined as the interval between the initial time point of assessment when no symptoms was reported and the subsequent time point of assessment when symptoms re-occurred before symptoms re-occurred. Subjects who have no B-symptoms and alive will be censored at the last B-symptom assessment prior to subsequent therapy initiated. This will be summarized descriptively.

    - Time to resolution (applicable to subject with symptom at baseline) is defined as the duration from baseline to the first time point when no symptom was reported. It will be summarized descriptively for those subjects who experienced resolution.

    - As an exploratory analysis, subject's best response, will be summarized for those who experienced resolution.

5. SAFETY

Safety will be analyzed using the incidence, intensity, and type of adverse events, laboratory tests. All safety analyses will be based on the safety analysis set.

5.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in NCI common toxicity criteria for adverse events (CTCAE) Version 4.03.

Treatment-emergent adverse events are 1) adverse events that occur after the first dose of study treatment, and up to + 30 days after last ibrutinib or up to 100 days after last dose of nivolumab whichever is last, or the start date of a subsequent systemic anticancer therapy, whichever is earlier (including both dates), 2) any adverse event that is considered study treatment - related (at least relationship to one drug of combination will be considered related) (i.e., possibly, probably, or very likely related to study drug) regardless of the start date of the event, 3) any adverse event that is present at baseline but worsens in severity and is subsequently considered drug-related by the investigator.

Treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term (PT), by severity, by relationship to study treatment, and by action taken. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by frequency in incidence (from the highest to lowest incidence). The same summary will be provided for drug-related adverse events, serious adverse events, and drug-related serious adverse events, immune-related events as well as adverse events leading to treatment discontinuation, and death.

5.2. Adverse Events of Special

Adverse events of special interest to be summarized include the following:

Major Hemorrhage

Hemorrhage SMQ without labs will be used to identify bleeding events. Any grade ≥3 hemorrhage events, any SAE or all grades of CNS hemorrhage (preferred terms are listed in Appendix A). Events will be summarized by preferred terms.

5.3. Adverse Events of Clinical Interest

Other Malignancies

New malignant tumors including solid tumors, skin malignancies and hematologic malignancies that occur after study treatment initiated will be identified and summarized by preferred terms and toxicity grade. Terms to be extracted are determined through cumulative AE term reviews.

Atrial Fibrillation

Cardiac events – Atrial fibrillation will be extracted by preferred terms. The number and percentage of subjects who had events will be summarized by preferred terms.

Ocular Events

Ocular events will be extracted and summarized separately by preferred terms.

Immune-related AEs (irAEs): Endocrine, Gastrointestinal, Hepatic, Hypersensitivity/Infusion Reaction, Pulmonary, Renal, Skin, and Visual Events

Immune-related events will be extracted (as below) and summarized separately by preferred terms.

CATEGORY	SUBCATEGORY	PREFERRED TERMS
ENDOCRINE ADVERSE EVENT	ADRENAL DISORDER	ADRENAL UNSUFFICIENCY
		ADRENAL SUPPRESSION
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
		HYPOTHALAMIC PITUITARY ADRENAL AXIS SUPPRESSION
		SECONDARY ADRENOCORTICAL INSUFFICIENCY
	DIABETES	DIABETES MELLITUS
		DIABETIC KETOACIDOSIS
		FULMINANT TYPE 1 DIABETES MELLITUS
		LATENT AUTOIMMUNE DIABETES IN ADULTS
		TYPE 1 DIABETES MELLITUS
	PITUITARY DISORDER	HYPOPHYSITIS
	THYROID DISORDER	AUTOIMMUNE THYROIDITIS
		BLOOD THYROID STIMULATING HORMONE DECREASED
		BLOOD THYROID STIMULATING HORMONE INCREASED
		HYPERTHYROIDISM
		HYPOTHYROIDISM
		PRIMARY HYPERTHYROIDISM
		PRIMARY HYPOTHYROIDISM
		THYROID FUNCTION TEST ABNORMAL
		THYROID HORMONES DECREASED
		THYROID HORMONES INCREASED
		THYROIDITIS
		THYROIDITIS ACUTE
		THYROXINE DECREASED
		THYROXINE FREE DECREASED
		THYROXINE FREE INCREASED
		THYROXINE INCREASED
		TRI-IODOTHYRONINE UPTAKE INCREASED

GASTROINTESTINAL ADVERSE EVENT	AUTOIMMUNE COLITIS
	COLITIS
	COLITIS ULCERATIVE
	DIARRHOEA
	ENTERITIS
	ENTEROCOLITIS
	FREQUENT BOWEL MOVEMENTS
	GASTROINTESTINAL PERFORATION
HEPATIC ADVERSE EVENT	ACUTE HEPATIC FAILURE
	ALANINE AMINOTRANSFERASE INCREASED
	ASPARTATE AMINOTRANSFERASE INCREASED
	AUTOIMMUNE HEPATITIS
	BILIRUBIN CONJUGATED INCREASED
	BLOOD ALKALINE PHOPHATASE INCREASED
	BLOOD BILIRUBIN INCREASED
	DRUG-INDUCED LIVER INJURY
	GAMMA-GLUTAMYLTRANSFERASE INCREASED
	HEPATIC ENZYME INCREASED
	HEPATIC FAILURE
	HEPATITIS
	HEPATITIS ACUTE
	HEPATOTOXICITY
	HYPERBILIRUBINAEMIA
	LIVER DISORDER
	LIVER FUNCTION TEST ABNORMAL
	LIVER INJURY
	TRANSAMINASES INCREASED
HYPERSENSITIVITY/INFUSION REACTION	ANAPHYLACTIC REACTION
	ANAPHYLACTIC SHOCK
	BRONCHOSPASM
	HYPERSENSITIVITY
	INFUSION RELATED REACTION
PULMONARY ADVERSER EVENT	ACUTE RESPIRATORY DISTRESS SYNDROME
	ACUTE RESPIRATORY FAILURE
	INTERSTITIAL LUNG DISEASE
	LUNG INFILTRATION
	PNEUMONITIS
RENAL ADVERSER EVENT	ACUTE KIDNEY INJURY
	BLOOD CREATININE INCREASED
	BLOOD UREA INCREASED
	CREATININE RENAL CLEARANCE DECREASED
	HYPERCREATININAEMIA
	NEPHRITIS
	NEPHRITIS ALLERGIC

	NEPHRITIS AUTOIMMUNE
	RENAL FAILURE
	RENAL TUBULAR NECROSIS
	TUBULOINTERSTITIAL NEPHRITIS
	URINE OUTPUT DECREASED
SKIN ADVERSE EVENT	AUTOIMMUNE DERMATITIS
	BLISTER
	DERMATITIS
	DERMATITIS EXFOLIATIVE
	DRUG ERUPTION
	ECZEMA
	ERYTHEMA
	ERYTHEMA MULTIFORME
	EXFOLIATIVE RASH
	PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME
	PHOTOSENSITIVITY REACTION
	PRURITUS
	PRURITUS ALLERGIC
	PRURITUS GENERALISED
	PSORIASIS
	RASH
	RASH ERYTHEMATOUS
	RASH GENERALISED
	RASH MACULAR
	RASH MACULO-PAPULAR
	RASH PAPULAR
	RASH PRURITIC
	SKIN EXFOLIATION
	SKIN HYPOPIGMENTATION
	SKIN IRRITATION
	STEVENS-JOHNSON SYNDROME
	TOXIC EPIDERMAL NECROLYSIS
	URTICARIA
	VITILIGO
VISUAL AE	UVEITIS
	VISION BLURRED
	ENDOPHTHALMITIS
	PHOTOSENSITIVITY REACTION
	VISUAL IMPAIRMENT
	PHOTOPSIA
	VISUAL FLOATERS
	PHOTOPHOBIA
	DIPLOPIA

Adverse events of interest and other safety observations will be summarized by disease type and study cohorts.

5.4. Death

A summary of the number of deaths since first administration of study agent up to + 30 days after last ibrutinib or up to 100 days after last dose of nivolumab whichever is last, will be provided, along with the primary cause of death. A death is a study drug-related death if the primary cause is a drug-related adverse event.

5.5. Clinical Laboratory Tests

Laboratory data for hematology and serum chemistry tests, up to the later of the End of Treatment visit or up to + 30 days after last ibrutinib or up to 100 days after last dose of nivolumab whichever is last, will be reported in SI units. Applicable laboratory results will be graded according to NCI-CTCAE Version 4.03. Toxicity grading for creatinine increase is based on the NCI-CTCAE v4.03 criteria but limited only to the part based on the ULN, the other part that is based on change from baseline is not used for toxicity grading. Toxicity grading for all other lab parameters are based on the NCI-CTCAE v4.03 criteria as is.

The following laboratory tests will be analyzed:

- Hematology: hemoglobin, white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count
- Chemistry: sodium, potassium, magnesium, creatinine, creatinine clearance (CrCl), AST, ALT, alkaline phosphatase, LDH, total bilirubin, albumin, amylase and lipase.
- Beta2-microglobulin, serum immunoglobulin levels (IgG, IgM, IgA): only for FL and CLL/SLL disease cohorts.
- Coagulation panel: PT APTT and INR
- Thyroid function: T3 free T4 and TSH

Descriptive statistics (mean, standard deviation, median, and range) will be calculated for the raw data and for change from baseline at each time point of assessment, as well as for change from baseline to the last value. Worst toxicity grade will be summarized for all hematology and chemistry parameters except for LDH, which will be summarized by abnormal/normal using normal ranges. Change from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters.

Lymphocytosis is defined as ALC increasing $\geq$ 50% from baseline and achieving level $\geq 5x10^9$ /L. Descriptive statistics will be provided for time to first lymphocytosis, i.e., time from first dose to date of first lymphocytosis. Similar to duration of response, Kaplan-Meier method will be used to estimate duration of first lymphocytosis as the time from first lymphocytosis to the earliest date of its resolution (i.e., when ALC decreased to the baseline level or lower or achieving level of $< 5x10^9$ /L) or date of censoring (i.e., date of last non-missing ALC).

5.5.1. Creatinine Clearance

Creatinine clearance (CrCl) is calculated using the Cockroft-Gault formula:

$$CrCl_{(est)} = \frac{(140 - age[yr])(lean\ body\ wt[kg])}{(72)(serum\ creatinine[mg/dL])} \times 0.85 (if\ female)$$

for males, the factor is 1 instead of 0.85

5.6. Other Safety Parameters

Change in ECOG scores from baseline to the worst score during the treatment will be provided as shift tables.

Subjects with more than 10% weight loss from baseline will be summarized.

- Change in ECG (QTcF only) from baseline to the worst score during the treatment will be provided as shift tables
- Listing of transfusion dependency by subject
- Listing of requirement of gCSF by subject

6. Pharmacokinetics

The plasma concentration data for ibrutinib and, if possible and judged relevant, PCI-45227 and other metabolites, if possible, will be summarized at each time point using descriptive statistics.

Population pharmacokinetic analysis of plasma concentration-time data will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant structural population-based pharmacokinetic model. Available subject characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. Details will be given in a population pharmacokinetic analysis plan and the results of the population pharmacokinetic analysis will be presented in a separate report.

Data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic (e.g., incomplete administration of the study agent; concentration data not sufficient for pharmacokinetic parameter calculation due to missing pharmacokinetic draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each dosage, descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the ibrutinib and PCI-45227 plasma concentrations at each sampling time and for all pharmacokinetic parameters of ibrutinib.

7. Biomarker

7.1. Biomarker Objectives

Inhibition of BTK tyrosine phosphorylation by ibrutinib has been shown to abrogate downstream survival pathways (eg, ERK1/2, PI3K, NF-kB, and MAPK). Inhibition by ibrutinib also interferes with activation of integrins and chemokine networks leading to interference with adhesion, migration, and homing of malignant cells. It is anticipated that subjects with alterations in BCR-signaling components or activation of alternative signaling pathways may have differential response to treatment.

7.2. Biomarker Analysis Sets

This population consists of all subjects who receive at least 1 dose of study drug (either ibrutinib or nivolumab). Subjects from this population will be analyzed if they received the treatment, have data from at least one of the clinical endpoints and also have data from any biomarkers. The biomarker population is defined as having at least one assay among all the results.

7.3. Biomarker Stratification Groups

Biomarker analysis will be performed with no patient stratification (all patients) and with stratification by dose expansion cohort by indication (i.e., biomarker stratification cohort) as shown:

A. CLL

B. CLL only del 17p

C. CLL only del 11q

D. FL

E. DLBCL

F. ABC-DLBCL (if available)

G. GCB-DLBCL (if available)

H. Richter Syndrome

I. ABC-like Richter's (if available)

J. GCB-like Richter's (if available)

7.4. Biomarker Tested

- IHC of PDL1, NGS and GEP (if available)

  PDL1 protein levels will be examined on tumor cells by Immunohistochemistry (IHC).

  FFPE slides from screening will be examined by IHC for PDL1 Staining. Cut points are listed

Biomarker Type	Biomarker	Description	Levels (Cutpoints)	Data column
IHC	PDL1	PDL1 option 1	Not elevated <5% Elevated ≥5%	PERCENT OF VIABLE TUMOR CELLS THAT EXHIBIT PD-L1 MEMBRANE STAINING
IHC	PDL1	PDL1 option 2	Negative = 0 Positive >0	PERCENT OF VIABLE TUMOR CELLS THAT EXHIBIT PD-L1 MEMBRANE STAINING
NGS	CARD11	Mutation	Positive Negative	
NGS	Additional genes ~5	Mutations	Positive Negative	
GEP (if available)	Genes ~10	Expression	>Median <=Median calculated within disease group	

- T cell Panel

  The following flow cytometry T-cell panel will determine a percentage and absolute numbers of each cell type at multiple time points (C1D1, C1D7, C3D1 and End of Treatment (EOT) or Progression (PRO):

  1. Absolute lymphocyte counts
  2. Viable CD3+, % of Single Lymphocytes
  3. Variable CD3+, Counts
  4. CD4% of CD3
  5. CD8% of CD3
  6. TH17, % of CD4+
  7. Treg, % of CD4+
  8. CD4+ICOS+, % of CD4+
  9. CD4+OX40+, % of CD4+
  10. CD4+PD-1+, % of CD4+
  11. CD8+ICOS+, % of CD8+
  12. CD8+OX40+, % of CD8+

13. CD8+PD-1+, % of CD8+

These values need to be calculated:

14. CD4 Counts
15. Treg Counts
16. TH17 Counts
17. CD4/OX40 Counts
18. CD4/PD-1 Counts
19. CD4/ICOS Counts
20. CD8 Counts
21. CD*/OX40 Counts
22. CD8/PD-1 Counts
23. CD8/ICOS Counts

7.5. Association Analysis of Biomarkers with Clinical Efficacy Endpoints

The primary endpoint is ORR, defined as the proportion of subjects who achieve partial response or better [PR(+L) or better], as assessed by the investigators at or prior to initiation of subsequent anti-cancer therapy. The primary efficacy analysis of ORR will be conducted at performed 6 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. The analysis will be based on the response-evaluable or biomarker populations, as see appropriate.

In addition, the following secondary endpoints will be evaluated if there are sufficient events to warrant the analysis:

- Duration of Response.
- Time to Response.
- Progression-free Survival and Overall Survival.
- Best overall Response.

7.5.1. Level of Significance

All tests will be 1-sided. The primary efficacy endpoint will be tested at the overall significance level of 0.025. Nominal p-values will be presented for all statistical analyses, if applicable.

7.5.2. Missing Data Handling

If >90% of subjects have missing value for a particular biomarker, or if all subjects have the same value for a biomarker, then only the frequencies will be summarized and that biomarker will be removed from further analysis.

If a subject has missing data for a clinically defined endpoint, that subject will be excluded from that particular association analysis but included in other analyses where data is available.

7.5.3. Data Transformation and imputation

No transformation will be performed on any of the clinical data other than what was transformed as part of the clinical statistical analysis. If deemed applicable, biomarker data may be log (base 2 or 10) transformed if the data distribution is not normal or otherwise skewed. Shapiro-Wilk's test will be used to determine normality for baseline only.

7.5.4. Outlier Detection and Handling

No outlier handling will be performed

7.5.5. Biomarker Data Analysis Methods for PDL1, and NGS and GEP (if available)

- Median, mean (SD), and range for continuous variable or N and frequency (%) for categorical variables will be reported for all-treated versus the biomarker populations for selected demographic and baseline characteristic variables including the biomarker stratification cohorts.

- The number of subjects (N) and the associated percentage (%) will be presented to facilitate the evaluation of the response rate. The median duration of response (arising from Kaplan -Meier estimate) between 1) PDL1 IHC option 1/2 subgroups (i.e., not elevated/negative vs. elevated/positive); 2) NGS subgroups (i.e., negative vs. positive); 3) GEP subgroups (i.e., >median vs. <=median) will also be reported.

  The relationship between 1) PDL1 not elevated (or negative) vs. elevated (or positive) subgroups; 2) NGS negative vs. positive subgroups; 3) GEP subgroups >median vs. <=median subgroup for duration of response, progression-free survival and overall survival will be evaluated by the Kaplan-Meier method. If the number of subjects is ≤7 then Kaplan-Meier analyses are unnecessary.
- For each of the biomarker stratification cohort, Fisher exact test will be used to test the association on the response between 1) PDL1 subgroups (not elevated and elevated for option 1; negative and positive for option 2); 2) NGS subgroups (negative vs. positive); 3) GEP subgroups (>median vs. <=median)
- Descriptive summary statistics [i.e., mean (SD), median and range] will be used to evaluate time to initial response and best response of the PDL1, NGS and GEP subgroups for each of the biomarker stratification cohort.

7.5.6. Biomarker Data Analysis Methods for Flow Cytometry T-cell Type Panel Data

- Data arisng from T-cell type panel collected over time will be descriptively summarized for each biomarker stratification cohorts. The corresponding mean (± se) over time line plot for each biomarker stratification cohorts will be generated. In Addition, mean change and percent change from baseline will also be descriptively summarized. The corresponding mean change and percent change from baseline values will be plotted.

- Mean values for each T- cell type over times by response group (i.e., non-responder and responder) will be reported for the biomarker stratification groups − CLL, FL, DLBCL, ABC-DLBCL, GCB-DLBCL and Richter's. For each cell type, the corresponding mean (± se) line and box plots over time by response group for each selected biomarker stratification group will be generated. Similarly, the mean (± se) line plot over time by progression group (i.e., progressor and non-progressor) for each cell type for selected biomarker stratification group will also be generated.

- Paired t-test will be performed to compare the mean at baseline vs the mean at each post baseline time point for each cell type and for each selected biomarker stratification group by respond group and progression group, respectively.

REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.
2. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.

APPENDICES

1. Appendix A

Preferred terms for CNS hemorrhage are as follows:

- Acute haemorrhagic leukoencephalitis
- Basal ganglia haemorrhage
- Brain stem haemorrhage
- Brain stem haematoma
- Central nervous system haemorrhage
- Cerebellar haematoma
- Cerebellar haemorrhage
- Cerebral arteriovenous malformation haemorrhagic
- Cerebral haematoma
- Cerebral haemorrhage
- Cerebral microhaemorrhage
- Encephalitis haemorrhagic
- Epidural haemorrhage
- Extradural haematoma
- Haemorrhage intracranial
- Haemorrhagic cerebral infarction
- Haemorrhagic stroke
- Haemorrhagic transformation stroke

- Intracerebral haematoma evacuation
- Intracranial haematoma
- Intracranial tumour haemorrhage
- Intraventricular haemorrhage
- Pituitary haemorrhage
- Putamen haemorrhage
- Ruptured cerebral aneurysm
- Spinal cord haemorrhage
- Spinal epidural haematoma
- Spinal epidural haemorrhage
- Spinal subarachnoid haemorrhage
- Spinal haematoma
- Spinal subdural haematoma
- Spinal subdural haemorrhage
- Subarachnoid haemorrhage
- Subdural haematoma
- Subdural haemorrhage
- Subgaleal haematoma
- Thalamus haemorrhage