Clinical Study Report Appendix 12.1.9	
Drug Substance	Acalabrutinib (ACP-196)
Study Code	ACE-LY-005

Appendix 12.1.9
Documentation of Statistical Methods and Supporting Statistical Analysis

Protocol Number: ACE-LY-005

Protocol Title: A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies

Version: 1.00

Version date: 17 January 2020

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas

PPD	28 March 2020
Prepared by PPD PPD	Date
PPD	30 March 2020
Approved by PPD PPD	Date
PPD	
Approved by PPD PPD	Date

Statistical Analysis Plan

A Phase 1b/2 Proof-of-Concept Study of the Combination of

ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies

Protocol Number: ACE-LY-005

Version: 1.00
Date:17 January 2020

Study Statistician: PPD

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TABLE OF ABBREVIATIONS

ACP-196	acalabrutinib
AE(s)	adverse event(s)
ATC	anatomical therapeutic chemical
BID	twice per day
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capturing
EORTC	European Organisation for Research and Treatment of Cancer
FL	follicular lymphoma
GCB	germinal center B-cell
IPD	important protocol deviation
MCL	mantle cell lymphoma
CCI	CCI
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MM	multiple myeloma
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response

PT	preferred term
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SLL	small lymphocytic lymphoma
TEAE(s)	treatment-emergent adverse events
US	United States
WHO	World Health Organization
WM	Waldenström macroglobulinemia

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the planned statistical analyses that have been outlined within Protocol Amendment 6 for Study ACE-LY-005, which is entitled "A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies" dated 14 March 2019. Any changes to the methods described in the final SAP will be documented in the clinical study report (CSR). Hereafter, acalabrutinb (a generic name for ACP-196) will be used in place of ACP-196 in this document.

Separate reports will be generated for pharmacokinetic (PK) and pharmacodynamics (PD) data.

2 OBJECTIVES

2.1 Primary Objectives

- To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with hematologic malignancies.

2.2 Secondary Objectives

- To evaluate the activity of acalabrutinib and pembrolizumab as measured by response rate, duration of response, progression-free survival, overall survival, and time to next treatment.

2.3 Exploratory Objectives:

CCI

[redacted]

3 STUDY OVERVIEW

3.1 Study Design

This is a Phase 1b/2, open-label, nonrandomized study that will be conducted in 2 stages. In the first stage, Part 1 of the study will determine the safety and preliminary

efficacy of acalabrutinib and pembrolizumab in a limited group of B-cell malignancies. In the second stage, Part 2 allows for possible expansion cohorts into a wider range of B-cell malignancies, and Part 3 (enrolled concurrently with Part 2) will evaluate the combination in subjects with myelofibrosis (MF).

Part 1

Six subjects will be enrolled to receive acalabrutinib in combination with pembrolizumab. If the combination is safe with ≤ 1 dose-limiting toxicity (DLT) (6-week observation period) in the first 6 subjects, the cohort will be expanded up to 24 subjects to obtain additional safety information and to assess the efficacy of the combination.

Part 1 of the study will include adult subjects with the following disease types:

- Non-GCB diffused large B-cell lymphoma (DLBCL)
- Follicular lymphoma (FL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)

Part 2

Part 2 consists of expansion groups of up to 30 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted. The possible expansion groups for Part 2 could include adult subjects with the following disease types:

- Non-GCB DLBCL
- GCB DLBCL
- Richter syndrome (RS)
- Mantel cell lymphoma (MCL)
- Non-Hodgkin lymphoma (iNHL)
    - FL
    - Waldenström Macroglobulinemia (WM)
    - CLL/SLL
- Multiple Myeloma (MM)
- Other B-cell malignancy (including but not limited to: Hodgkin's lymphoma, Burkitt lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia)

Under Amendment 3 of this protocol, subjects with MCL or iNHL (including FL, WM, and CLL/SLL) are no longer enrolled. Under Amendment 4, subjects with RS are no longer enrolled.

Part 3

Part 3 includes up to 30 subjects with primary MF, post-polycythemia vera MF, or postessential thrombocythemia MF with thrombocytopenia or anemia. Part 3 will run in parallel with Part 2. Subjects with MF will receive a run-in of 6 weeks of acalabrutinib alone.

Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will be treated with combination therapy with acalabrutinib and pembrolizumab.

In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (i.e., the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If < 2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of “clinical improvement” or better. the MF group will not be expanded. The decision to expand the study is multifactorial and will take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects.

Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

All Parts

Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled.

Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study. Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab, provided subjects are tolerating the drug and not progressing. In addition, pembrolizumab treatment can end for subjects with confirmed complete remission (CR) (or stringent complete remission [sCR] for MM) if treatment has been

administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR/sCR. Subjects who have **confirmed** progressive disease will come off treatment. Note: If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (eg, for drug related toxicity or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

All subjects will have bone marrow biopsy, hematology, chemistry, thyroid, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, hematology, and thyroid function tests, once weekly for the first 8 weeks, followed by a Week 10 visit and then every 3 weeks thereafter (every 6 weeks thereafter for thyroid function tests) through Week 103. For subjects who discontinue pembrolizumab at Week 103, the Week 103 visit will be followed by Week 106 and Week 109 visits, at which time, the investigator will determine eligibility to continue single-agent acalabrutinib treatment. Subjects remaining on study treatment after Week 103 will have a Week 103 and Week 115 visit, and then visits for safety and tumor response assessments every 24 weeks starting at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies).

Subjects who permanently discontinue pembrolizumab at any time during study participation must have a minimum of 2 consecutive study visits, 3 weeks apart, after the last dose of pembrolizumab for safety evaluation. The study visits will be scheduled as follows:

- For all subjects except MM and CLL subjects

  - If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.

- If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, 2 consecutive study visits will be held 3 weeks apart (eg, Week 40 and 43), after which study visits will be held every 12 weeks.

- It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study visit schedule with the radiologic tumor assessment schedule, the first 2 study visits after pembrolizumab discontinuation should be 3 and 6 weeks after pembrolizumab discontinuation and then scheduled to align with the nearest radiological timepoint.

• For CLL subjects

- If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.

- If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 12 weeks.

- It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study visit schedule with the radiologic tumor assessment schedule, the first study visit should be scheduled to align with the nearest radiological timepoint. In addition, subjects who permanently discontinue pembrolizumab for any reason (eg, pembrolizumab toxicity, AE, or completing the 103-week course of pembrolizumab) and remain on acalabrutinib alone at any time during study participation must have a thyroid test done every 6 weeks for 6 months after pembrolizumab discontinuation. Thyroid testing may be discontinued at 6 months if 1) testing that was performed at 6 months was normal and 2) testing that was performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue as scheduled until 2 consecutive normal test results.

Refer to protocol Appendix 5 and Appendix 6 for a comprehensive list of study assessments and their timing.

3.2 Sample Size

In Part 1 (dose-limiting toxicity [DLT] review), enrollment of 6 subjects for DLT review is consistent with sample sizes used in oncology studies for determination of maximum toxicity dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in < 33.3% of subjects). Provided $\leqslant$ 1 DLT occurs during the DLT review, then expansion will occur in Part 1 to include up to 24 subjects in a select group of histologies. The safety and preliminary efficacy results from Part 1 will be used to determine opening Part 2 and Part 3 of the protocol.

In Part 2 (expansion groups), enrollment of 30 subjects offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types. An ORR of $\geqslant$ 20% is considered the minimum value of potential interest in each of the selected indications. If < 2 subjects per cohort experience an objective response, the probability is > 0.90 that an ORR of ≥ 20% will be excluded for that cancer. If 2 subjects in a group experience an objective response, the upper bound of a 1-sided exact binomial 90% CI = 16.8%.

In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (ie, the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If < 2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of “clinical improvement” or better, the myelofibrosis (MF) group will not be expanded. The decision to expand the study is multifactorial and needs to take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects.

Table 3-1 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of all possible values for the observed response rate in the initial group of 12 subjects.

Table 1. Two-Sided Exact 90% CIs for Response Rate in Initial Group in Part 3 (N=12)

Responses, n	Response Rate, %	90%CI	
		Lower Bound	Upper Bound
0	0%	0%	22%
1	8%	0%	34%
2	17%	3%	44%
3	25%	7%	53%
4	33%	12%	61%
5	42%	18%	68%
6	50%	25%	75%
7	58%	32%	82%
8	67%	39%	88%
9	75%	47%	93%
10	83%	56%	97%
11	92%	66%	100%
12	100%	78%	100%

Abbreviation: CI = confidence interval.

If the MF group is expanded, enrollment of 30 subjects offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in MF. A response rate (clinical improvement, PR, or CR) of $\geqslant$ 25% within the sample size of 30 subjects with MF is considered the minimum value of potential interest in this highly unmet medical need population of MF patients with thrombocytopenia or anemia. To reject the null hypothesis of response rate $\leqslant$ 5% in favor of an alternative hypothesis that the response rate is $\geqslant$ 25%, 30 subjects will preserve approximately 90% power to detect the difference at a 0.05 level of significance by 1-sided exact test for single proportion. Considering the planned expansion cohort size of 30 subjects, Table 3-2 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of all possible values for the observed response rate.

Table 3-2. Two-Sided Exact 90% CIs for Response Rate in Expansion Cohorts in Part 2 and Part 3 (N=30)

Responses, n	Response Rate, %	90%CI	
		Lower Bound	Upper Bound
0	0%	0%	10%
1	3%	0%	15%
2	7%	1%	20%
3	10%	3%	24%
4	13%	5%	28%
5	17%	7%	32%
6	20%	9%	36%
7	23%	11%	39%
8	27%	14%	43%
9	30%	17%	47%
10	33%	19%	50%
11	37%	22%	53%
12	40%	25%	57%
13	43%	28%	60%
14	47%	31%	63%
15	50%	34%	66%
16	53%	37%	69%
17	57%	40%	72%
18	60%	43%	75%
19	63%	47%	78%
20	67%	50%	81%
21	70%	53%	83%
22	73%	57%	86%
23	77%	61%	89%
24	80%	64%	91%
25	83%	68%	93%
26	87%	72%	95%
27	90%	76%	97%
28	93%	80%	99%
29	97%	85%	100%
30	100%	90%	100%

Abbreviation: CI=confidence interval.

4 STUDY ENDPOINTS

4.1 Safety Endpoints

- Frequency and severity of treatment-emergent AEs/SAEs.
- Relationship of AEs to study drug (eg, either acalabrutinib, pembrolizumab, or both).
- Change of laboratory parameters from baseline over time.
- Vital sign assessments, ECGs, and physical examinations

4.2 Efficacy Endpoints

- Response rate
- Duration of response
- Progression-free survival
- Time-to-next treatment
- Overall survival

4.3 PD or Biomarker Analysis

Additional PD and biomarker analyses may be performed, as deemed appropriate.

5 HYPOTHESES AND MULTIPLICITY

No formal statistical hypothesis will be tested. The clinical hypothesis is that acalabrutinib and pembrolizumab is safe and effective in subjects with hematologic malignancies.

6 ANALYSIS SUBSETS

6.1 All Treated Population

The safety analyses and primary efficacy analyses will be performed on the All-treated population, defined as all enrolled subjects who receive ≥1 dose of any study drug (either acalabrutinib or pembrolizumab).

6.2 Efficacy-evaluable Population

All subjects in the All-treated population who have $\geqslant$ 1 evaluable response assessment after the first dose of study drug (either acalabrutinib or pembrolizumab). Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.

7 INTERIM ANALYSIS

No formal interim analysis was planned.

8 MISSING VALUES

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for initial diagnosis is on or after date of first dose, the date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

9 STATISTICAL METHODS OF ANALYSIS

9.1 General Principles

Descriptive statistics will be used to summarize baseline demographic and disease characteristics, study drug administration, efficacy and safety outcomes. Descriptive summaries of discrete data will present the sample size and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present

the sample size, group mean, standard deviation (SD), median, and range. Confidence intervals (CIs) may be included as appropriate.

Summary tables will be presented by disease types: CLL/SLL, MCL, WM, FL, GCB DLBCL, MM, non-GCB DLBCL, RICHTER's and Other (include unclassifiable DLBCL, double hit lymphoma, FL with transformation, mediastinal DLBCL, mediastinal gray zone lymphoma, non-hodgkin's lymphoma [NHL], non-mediastinal gray zone lymphoma, red pulp small B-cell lymphoma, triple hit high grade NHL, hodgkin's lymphoma, marginal zone lymphoma), unless otherwise stated.

9.2 Subject Accountability

Subject disposition will be summarized for all treated subjects including the following information:

- Subject status on acalabrutinib and pembrolizumab
- Count and reason separately for acalabrutinib and pembrolizumab discontinuation
- Subject status for the study
- Count and reason for study termination
- Time on study
- Number of death

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the summary of IPDs table and the list of subjects with IPDs.
The listing of the final IPD will be provided.

9.4 Baseline Data

Summaries of demographics and baseline characteristics will be presented for subjects in the all treated population. For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, number and percentage of subjects in each category will be summarized.

9.4.1 Demographics

- Sex (Male, Female)
- Age (continuous)
- Age category (≥ 65)
- Ethnicity
- Race

9.4.2 Baseline Characteristics

- Height (cm)
- Weight (kg)
- ECOG performance status at baseline
- Bulky disease (grouped as ≥ 5 and ≥ 10 cm)
- Baseline B-symptoms (weight loss, fever and night sweats)
- Baseline Rai stage (CLL/SLL)
- Baseline Ann Arbor stage

9.5 Treatment and Medications

9.5.1 Prior Anticancer Therapies

A prior anticancer therapy is defined as a systemic therapy subjects received, either as a single or combination therapy, for the treatment of active corresponding target disease with a start and end date occurring before the date of first dose of study treatment. Therapies given as a consolidation or maintenance of a response or remission will not be considered as a separate regimen. The number of lines and type of prior therapy will be summarized according to each disease cohort.

9.5.2 Prior and Concomitant Medications Received for Indications Other than Target Disease

Data reported on concomitant CRF page will be used. Medications started or ended prior to first dose will be consider as prior treatment. Concomitant therapy is defined as all medications used on or after the first dose, through the treatment phase, and for 30 days following the last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant. Start date and end date will be imputed based on the rules provided in Section **12.1.** of the SAP. Medications with completely missing start and stop dates will be considered as concomitant medications.

Prior and concomitant medications other than antineoplastic agents or other systemic therapies after enrollment will be summarized by the World Health Organization (WHO) Drug Dictionary therapeutic class, pharmacological class, and preferred term by each disease area.

9.5.3 Exposure to Study Drug

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize regarding the number of acalabrutinib doses prescribed:

- Total number of doses taken
- Duration of exposure (the interval between first dose date and last dose date)
- Average daily dose (the ratio of total dose administered and treatment duration)
- Relative dose intensities (the ratio of average daily dose and prescribed doses)
- The number and timing of prescribed dose reductions and interruptions

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize regarding the number of acalabrutinib doses prescribed:

- Total number of doses taken
- Duration of exposure (the interval between first dose date and last dose date)
- Average dose per cycle (total dose administered per cycle)
- Relative dose intensities (the ratio of average daily dose and prescribed doses)
- The number and timing of prescribed dose reductions and interruptions
-

9.6 Analyses of Efficacy Endpoints

9.6.1 Response Rate

9.6.1.1 Definition

ORR will be defined as the proportion of subjects who achieve a response defined in Section 4.2 in protocol for different disease. For lymphoma, response means partial response (PR) or better, for WM subjects response means miner response (MR) or better, for subjects with MF, response including clinical improvement or better (clinical improvement, PR, or CR). Please refer to Protocol section 4.2 for the detail information and definition of the response.

9.6.1.2 Analysis Methods

The primary analysis of ORR will be conducted on the all treated population. A descriptive analysis will be done on for subgroups of subjects who receive acalabrutinib alone or the combination of acalabrutinib and pembrolizumab. ORR and the corresponding 90% and 95% two-sided CI calculated using exact methodto the binomial distribution will be presented.

The number and proportion of subjects within each category of response as well as the associated 95% CIs will be presented. The proportion will be estimated by dividing the number of subjects within each category of response by the total number of subjects in the analysis population. Each subject will be counted within only one response group, with the best response during the study as the classification group.

In addition, for subjects with CLL/SLL in Parts 1 and 2, a response will be assessed according to Table 4-2, which reflects modified International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include PRL. For the purpose of this analysis, lymphocytosis at a given timepoint will be defined as absolute lymphocyte count which is above normal limits and is not $\geqslant$ 50% decreased from baseline. For Part 3 subjects with MF, an additional analysis will evaluate response when defined as CR + PR only.

9.6.2 Duration of Response

The duration of overall response (DOR) defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. Subjects who had the event after the start of subsequent therapy, or are progression-free and alive at the time of data cutoff, or have unknown status will be censored at the last tumor assessment on or before the start of subsequent therapy and data cut-off time. The censoring rules for DOR are summarized in Appendix 12.2. The summary of DOR including mean, minimum, maximum, Q1 and Q3 are provided for all the responders for each disease group.

9.6.3 Progression-free Survival

Progression-free survival (PFS) is defined as the interval from the first dose date of acalabrutinib or pembrolizumab to the earlier of the first documentation of objective disease progression or death from any cause. Subjects who had the event after the start of subsequent therapy, or who are progression-free and alive at the time of data cutoff, or have unknown status will be censored at the time of their last disease assessment on or before the start of subsequent therapy and data cut-off. Subjects with no post baseline disease assessment will be censored on Day 1. The censoring rules for primary and sensitivity analyses of PFS are summarized Appendix 14.4.

The summary of PFS including the mean, minimum, maximum, median, Q1 and Q3 are provided for all the responders for each disease group.

Summary of K-M estimates of PFS and 95% CIs as proper for each disease group

9.6.4 Time to Next Treatment

Time-to-next treatment defined as the time from the first dose date of acalabrutinib or pembrolizumab to the start of the next treatment other than the study treatment. Descriptive statistics will be presented.

The summary of time to next treatment including the mean, minimum, maximum, median, Q1 and Q3 are provided for all the responders who have the next treatment for each disease group.

9.6.5 Overall Survival

The duration of OS will be measured from the time of first study drug administration until the date of death from any cause. Subjects who are known to be alive as of their last known status will be censored at their last date known to be alive. Subjects who are lost in follow-up will be censored at the date the subject is last known to have been alive. The censoring rules for OS are summarized Appendix 14.5.

The summary of OS including the mean, minimum, maximum, median, Q1 and Q3 are provided for all the responders for each disease group.

Summary of 24 months K-M estimates of probability of OS including min, max, median and 95% CIs are provided for each group as well.

9.6.6 Analysis Methods

The analysis of DOR will be conducted on the subset of the All-treated Population who are defined as responder in protocol section 4.2. The analysis of PFS and OS will be conducted on the All-treated Population. The analysis of DOR, PFS, and OS will be estimated using the Kaplan-Meier (KM) method. KM estimates with 95% CIs will be calculated for event time quartiles, and event-free rates will be calculated at selected time points. In addition, the reason for censoring will be summarized for DOR, PFS and OS.

9.7 Analyses Safety Endpoints

Safety analyses will be performed on the All-treated Population.

9.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class and a preferred term. The severity of the AE will be assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. Drug-related AEs are those assessed by investigator as related.

Treatment-emergent AEs are defined as those events that occur (actual or imputed start date) on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug.

Treatment-emergent AEs will be summarized by system organ class and preferred terms in descending order of frequency, by NCI toxicity grade and by relationship to study drug. The same summary will be provided for serious treatment-emergent AEs and drug-related serious treatment-emergent AEs, treatment-emergent AEs leading to treatment discontinuation, dose reductions and dose withheld.

Death information is reported in the study exit CRF for all deaths. Incidences of deaths are to be reported, along with the primary cause of death.

AE by subject listing and death listing will be provided.

9.7.2 Laboratory Test Results

Laboratory data of hematology, serum chemistry up to 30 days after last dose or the safety follow-up visit date, whichever is later, will be reported in SI units. Applicable laboratory results will be graded according to CTCAE Version 4.03 or higher. Generic normal ranges will be applied whenever reference ranges are not available.

Shift from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters. Figures of changes in selected parameters will be plotted overtime as appropriate.

Urinalysis data will be summarized as appropriate.

By subject lab listing will be provided per each disease group.

9.7.3 Vital Signs

Summary statistics (mean, standard deviation, median, and range) will be produced for vital signs at baseline, maximum, change from baseline to maximum, last value, and change from baseline to last value.

In order to be included in the table, a subject must have both a baseline value and a value for the given post-baseline time point.

By subject lab listing will be provided per each disease group.

9.7.4 ECOG Performance Status

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

By subject ECOG listing will be provided per each disease group.

9.7.5 Physical Examinations

Physical examination data collected at screening and post-treatment will be summarized. Descriptive statistics will be calculated for each parameters.

By subject physical examination listing will be provided per each disease group.

10 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There is no major change from protocol-specified analyses.

11 LITERATURE CITATIONS / REFERENCES

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12 APPENDICES

12.1 Study day

The study day will be calculated in reference to the date of first dose date. Study Day 1 is defined as the date of first dose of any study drug. For assessments that occur on or after first dose date, study day is defined as (date of assessment – date of first dose + 1). For assessments that occur prior to first dose date, study day is defined as (date of assessment – date of first dose). There is no Study Day 0.

12.2 Censoring Rules for Duration of Response

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD on or before receiving subsequent anti-cancer therapy or data cutoff, whichever occurred first	Event	Date of Death	Death
New anti-cancer treatment Started before PD or death for subjects with or without documented PD or death and before data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anti-cancer treatment	New anti-cancer therapy
No documented PD or death at the time of data cutoff and subject not received subsequent anti-cancer therapy or subsequent anti-cancer therapy start date after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up

12.3 Censoring Rules for Progression-free Survival

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented PD on or before receiving subsequent anti-cancer therapy or data cutoff, whichever occurred first	Event	Date of Death	Death
death before first adequate disease assessment	Event	Date of Death	Death
New anti-cancer treatment Started before PD or death for subjects with or without documented PD or death and before data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anti-cancer treatment	New anti-cancer Therapy
No documented PD or death at the time of data cutoff and subject not received subsequent anti-cancer therapy or subsequent anti-cancer therapy start date after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Withdrew consent before documented PD or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up before documented PD or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No post-baseline adequate disease assessments	Censored	Date of first dose	No post-baseline adequate disease assessments
No baseline disease assessments	Censored	Date of first dose	No baseline disease assessment

12.4 Censoring Rules for Overall Survival

Situation	Outcome	Date	Event Description/ Censoring Reason
Death on or before data cutoff	Event	Date of death	Death
Death or alive on or after data cutoff	Censored	Date of data cutoff	Data cutoff
Withdrew consent prior to data cutoff	Censored	Date of discontinuation from study participation as reported on study exit CRF	Withdrew consent
Lost to follow-up prior to data cutoff	Censored	Date subject last known to be alive	Lost to follow-up
Survival status unknown on or after data cutoff	Censored	Date subject last known to be alive	Continue on study