Product: Acalabrutinib
Statistical Analysis Plan: Solid Tumor Studies
Version *1.0* dated: 30 January *2018*

Protocol Numbers: *ACE-ST-003, ACE-ST-005, ACE-ST-006, ACE-ST-007, ACE-ST-208*

Title: *A Master Statistical Analysis Plan for Solid Tumor Studies*

Version: 1.0

Version date: 30 January 2018

The undersigned have reviewed and approved this plan

[redacted]

[redacted]

Date

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Date

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Date

A Master Statistical Analysis Plan

for

Solid Tumor Studies including ST-003, ST-005, ST-006, ST-007, and ST-208

Version:	**Version 1.0**
Date:	***30Jan 2018***
Studies Statistician:	[redacted]

Table 1. A List of Applicable Studies Covered by This SAP

Protocol Number	Treatment groups	Indication	Phase	Protocol Title
ACE-ST-003	Acalabrutinib vs Acalabrutinib + Pembrolizumab	Pancreatic Cancer	2	A Phase 2 Proof-of-Concept Study of ACP-196 Alone and in Combination with Pembrolizumab in Subjects with Advanced or Metastatic Pancreatic Cancer
ACE-ST-005	Pembrolizumab vs Acalabrutinib + Pembrolizumab	Bladder Cancer	2	Randomized Phase 2 Trial of ACP-196 and Pembrolizumab Immunotherapy Dual CHECKpoint Inhibition in Platinum Resistant Metastatic Urothelial Carcinoma
ACE-ST-006	Pembrolizumab vs Acalabrutinib + Pembrolizumab	Head and Neck Cancer	2	A Phase 2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Advanced Head and Neck Squamous Cell Carcinoma
ACE-ST-007	Pembrolizumab vs Acalabrutinib + Pembrolizumab	Non-small Cell Lung Cancer	2	A Phase 2 Proof-of Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Advanced Non-small Cell Lung Carcinoma
ACE-ST-208	Acalabrutinib vs Acalabrutinib + Pembrolizumab	Ovarian Cancer	2	A Phase 2 Proof-of-Concept Study of ACP-196 Alone and in Combination with Pembrolizumab in Subjects with Recurrent Ovarian Cancer

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TABLE OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice per day
BMI	Body mass index
BOR	best overall response
CA19-9	cancer antigen 19-9 (carbohydrate antigen 19-9)
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HNSCC	head and neck squamous cell carcinoma
ICF	informed consent form
IPD	Important Protocol Deviation
ir	immune-related
irRECIST	immune-related response criteria
IV	intravenous or intravenously
MDSCs	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	pharmacodynamics
PD	progressive disease
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PR	partial response
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODRUG	World Health Organization WHO Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocols of [redacted] including *ST-003(pancreatic cancer), ST-005 (bladder cancer), ST-006 (head and neck squamous cell carcinoma, HNSCC), ST-007 (non-small cell lung cancer, NSCLC), and ST-208 (ovarian cancer)*. The scope of this plan includes the final analysis. Any changes to the methods described in this SAP will be documented in each clinical study report (CSR).

2. OBJECTIVES

2.1 Primary Objective

- To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with solid tumors in each of the five studies including ST-003 (pancreatic cancer), ST-005 (bladder cancer), ST-006 (HNSCC), ST-007 (NSCLC), and ST-208 (ovarian cancer).
- To determine the best overall response rate and overall response rate (ORR) of pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab. This applies to ST-005, ST-006 and ST-007.

2.2 Secondary Objective

- To evaluate the efficacy (multiple efficacy endpoints including ORR, PFS and OS) of acalabrutinib monotherapy and acalabrutinib and pembrolizumab combination treatment in subjects with solid tumors using standard response criteria. This applies to ST-003 and ST-208.
- To determine progression-free survival (PFS) in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab. This applies to ST-005, ST-006, and ST-007.
- To evaluate the overall survival (OS) in subjects treated with pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab. This applies to ST-005, ST-006, and ST-007.

2.3 [redacted]

- [redacted]

3. STUDY OVERVIEW

3.1 Study Design

These five studies are phase 2, multicenter, open-label, randomized studies evaluating acalabrutinib or pembrolizumab monotherapy and the combination of acalabrutinib and pembrolizumab in subjects with solid tumors. Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms:

Arm 1: Acalabrutinib 100 mg administered orally (PO) twice per day (BID) (ST-003, ST-208) **or** Pembrolizumab 200 mg administered as an intravenous (IV) infusion every 3 weeks (Q3W) (ST-005, ST-006, ST-007)

Arm 2: Acalabrutinib 100 mg PO BID plus Pembrolizumab 200 mg IV Q3W

Acalabrutinib treatment can continue for subjects who are tolerating therapy and not progressing. Pembrolizumab study treatment is for 24 months from the date of first dose for subjects who are tolerating therapy and not progressing. Subjects who have confirmed progressive disease on the combination of pembrolizumab and acalabrutinib will discontinue study treatment. Subjects who have confirmed progressive disease on monotherapy arm may start combination until a second disease progression. Disease progression will be determined based on irRECIST guidelines. Also pembrolizumab treatment can end for subjects with confirmed complete response (CR) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR.

Refer to Protocol section 3 for more details.

3.2 Sample Size

The planned sample sizes per arm for each of the studies are listed below. For sample size justification, reference corresponding study protocols:

Study	Arm 1: Acalabrutinib	Arm 1: Pembrolizumab	Arm 2: Acalabrutinib + Pembrolizumab
ST-003	38		38
ST-005		37	37
ST-006		37	37

ST-007		37	37
ST-208	38		38

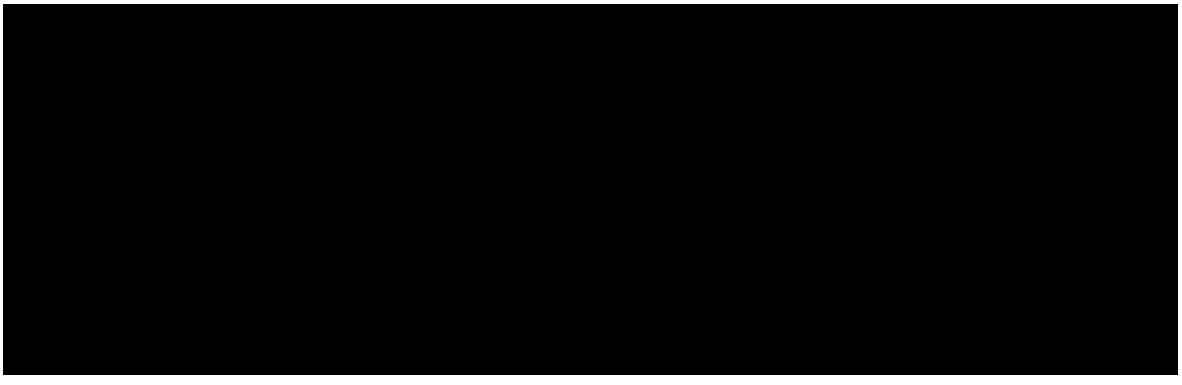
4. STUDY ENDPOINTS

4.1 Safety Endpoints

- Type, frequency, severity, timing of onset, duration, and relationship to either or both study drug of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), AEs leading to dose modification, dose delay and discontinuation of any study drug

4.2 Efficacy Endpoints

- Disease control rate (DCR) defined as stable disease (SD), partial response (PR) or CR based on modified RECIST 1.1 criteria. DCR by RECIST will be considered the primary endpoint of ST-003
- ORR, defined as PR or CR based on modified RECIST 1.1 criteria. ORR by RECIST will be considered the primary endpoint of ST-005, ST-006, ST-007, and ST-208
- Duration of response (DOR)
- PFS
- OS
- Change in serum cancer antigen CA-19-9. This applies to ST-003 only
- Change in serum cancer antigen CA-125. This applies to ST-208 only



5. HYPOTHESES AND MULTIPLICITY

This series of solid tumor studies are proof of concept studies. No formal hypothesis will be tested and no multiplicity adjustments will be made.

6. ANALYSIS SETS

The following definitions will be used for the efficacy and safety analysis populations.

6.1 Safety Analysis Set

The safety analysis set includes all subjects who receive at least one dose of any study drug (either acalabrutinib or pembrolizumab). The safety analysis set will be used for evaluating the safety and efficacy endpoints with the exception of DOR. The analyses of DOR will be conducted on the subset of the safety analysis set who achieve CR or PR as their best overall response.

6.2 Efficacy Evaluable Analysis Set

All subjects in the safety analysis set who have ≥ 1 evaluable response assessment after the first dose of study drug (either acalabrutinib or pembrolizumab). Sensitivity analyses of efficacy endpoints will be carried out on the efficacy-evaluable population.

6.3 Pharmacokinetic/Pharmacodynamic Analyses Set

Pharmacokinetic/Pharmacodynamic evaluable analysis set will be defined by PK/PD group.

7. FINAL ANALYSIS AND CLINICAL STUDY REPORT

Planned final analysis will be conducted once last subject exits study and database is locked. The CSR will be written based on the final analysis.

8. STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

Descriptive statistics [including means, standard deviations, medians, minimum and maximum for continuous variables and frequency, proportions and confidence intervals (CIs) for discrete variables] will be used to summarize data as appropriate.
Calculation of time to event or duration of event endpoints will be based on the study day of the event or censoring date rather than visit number or visit label. Missing efficacy or safety data will not be imputed unless otherwise specified.

The following rules will be used for the days to months/years conversion:

- 1 month= 30.4375 days;
- 1 year= 365.25 days.

All summaries will be presented by treatment group.

8.2 Subject Accountability

The number of subjects enrolled by site will be presented. Subject disposition will be summarized for all enrolled subjects including the following information:

- Proportion of subjects who received study drug
- Proportion of subjects with study drug discontinuation and primary reason for study drug discontinuation
- Proportion of subjects discontinuing study and reasons for study discontinuation
- Time on study

8.3 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. The final IPD list for each study is used to produce the summary of IPDs and the listing of subjects with IPDs, respectively.

8.4 Demographic and Baseline Characteristics

Summaries of demographic characteristics will be presented for age, age category (< 65, ≥ 65), gender, race, ethnicity, and geographic region for each study.
Baseline characteristics will be presented for Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, tumor grade where relevant, number of prior anticancer therapies for each study.

8.5 Treatment and Medications

8.5.1 Prior Anticancer Regimens

Summary statistics will be presented for prior anticancer regimens (might include multiple therapies) and prior cancer-related surgery for each study. Prior cancer therapy categories will be adjudicated by the medical monitor.

8.5.2 Concomitant Medications

Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

8.5.3 Exposure to Investigational Product

Number of subjects who received at least one dose of acalabrutinib, pembrolizumab or both, duration of exposure, average daily dose of acalabrutinib, average dose of pembrolizumab per administration cycle, and relative dose intensity will be summarized for each investigational product and by treatment group.
Exposure parameters are defined in more detail in Appendix 12.1.

8.6 Safety Analyses

8.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA v20.1 or higher) 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. Study drug-related AEs are those assessed by investigator as related.

All AE tables will be summarized by original treatment group and crossover group for each study. For subjects who crossed-over from monotherapy to a combination therapy of acalabrutinib and pembrolizumab, AEs experienced up to crossover date will summarized under monotherapy arm, while AEs on or after the cross-over date (1st dose date of second study drug added) will be summarized under crossover group.

TEAEs are defined as those events that occur or worsen on or after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of acalabrutinib or within 90 days following the last dose of pembrolizumab.

TEAEs will be summarized by system organ class (SOC) and preferred terms in descending order of frequency, by CTCAE toxicity grade. Drug-related TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation and removal from study will be summarized by SOC and preferred terms as well as by preferred teams only in descending order of frequency and by CTCAE toxicity grade.

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

8.6.2 Adverse Events of Clinical Interest

Events of Clinical Interest identified for acalabrutinib and combination of acalabrutinib with pembrolizumab will be summarized for each study. The definitions of these categories are part of Appendix 12.5 and 12.6.

8.6.3 Laboratory Test Results

Laboratory data 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. For each laboratory parameter, the baseline laboratory value/grade is defined as the last laboratory value/grade collected on or prior to the date of the first dose of study drug. Treatment-emergent laboratory abnormalities for selected parameters will be summarized.

8.6.4 Vital Signs

Body temperature, heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), and weight will be collected for each study as scheduled in protocol Appendix. For each parameter, summary statistics (mean, standard deviation, median, and range) will be produced for baseline, maximum, and minimum value.

8.6.5 ECOG Performance Status

ECOG performance status scores will be summarized for each treatment group using shift table. The shifts in scores from baseline to worst ECOG score on treatment will be summarized.

8.7 Efficacy Analyses

8.7.1 Best Overall Response, Disease Control Rate and Overall Response Rate

DCR is defined as the proportion of subjects who achieve a best response of SD, PR or CR at any point of the study. The primary endpoint for ST-003 is DCR by RECIST1.1 criteria by investigators.

ORR is defined as the proportion of subjects who achieve a best response of PR or CR at any point of the study. The primary endpoint for ST-005, ST-006, ST-007, and ST-208 is ORR by RECIST1.1 criteria by investigators.

The primary analysis of DCR and ORR will be conducted using safety analysis set. DCR and ORR will be calculated with the corresponding exact binomial 2-sided 95% CI for each original treatment arm and separately for subjects who crossed over from a monotherapy to a combination therapy. Monotherapy subjects who crossed-over will be summarized according to their original treatment assignment up to the point of crossover, and then summarized as a crossover subject using their response immediately prior to crossover as a new baseline for their combination treatment. A sensitivity analysis using efficacy evaluable analysis set will also be presented.

Descriptive statistics will be provided for best overall response for each treatment group. The number and proportion of subjects within each category of response will be presented.

8.7.2 Duration of Response

The DOR is 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. The DOR will only be summarized for subjects in safety analysis set who achieved response (CR or PR) at any point of the study. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median).

For crossover subjects who originally started on monotherapy, the DOR will only be summarized/listed if ORR for this group is non-zero. If confirmed response is achieved after the crossover, the DOR for a combination therapy will be summarized.

Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of the new antitumor therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date before the missing assessments which lack objective disease assessment. The details of definition of progression events and censoring rules are the same as for PFS endpoint and are listed in Appendix 12.3.

8.7.3 Progression-free Survival

Progression-free survival is defined as the interval from the start of therapy to the earlier of the first documentation of objective disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median).

For crossover subjects who originally started on monotherapy, the PFS will only be summarized/listed if ORR for this group is non-zero.

Data from surviving, non-progressing subjects will be censored at the date of the last adequate disease assessment that is on or before the start date of the new antitumor therapy. Data from subjects who have disease progression or die after more than one missed visit will be censored at the last visit date prior to the missing assessments which lack objective disease assessment. The details of definition of progression events and censoring rules for primary and sensitivity analyses of PFS are listed in Appendix 12.3.

In the primary analysis using safety analysis set, study treatment end date will be used as the date of progression for subjects who discontinued study treatment due to disease progression or death prior to 1st radiographic assessment. Data for subjects who discontinued study treatment prior to 1st radiographic assessment due to reasons other than disease progression or death will be censored at their study treatment start date.

8.7.4 Overall Survival

Overall survival is defined as the time from treatment start date until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who lost to follow-up for survival immediately after randomization will be censored at first dose date (Appendix 12.4). OS will be summarized for safety analysis set only and based on original treatment assignment. Crossover subjects who originally started on monotherapy and cross over to a combination treatment will be summarized as part of the original monotherapy group for OS. The analysis methods for OS will be similar to those described for PFS.

8.7.5 Serum Cancer Antigens CA-19-9 and CA-125

Changes in CA-19-9 (ST-003) and CA-125 (ST-208) will be evaluated using descriptive statistics using safety analysis set.

8.7.6 Exploratory Efficacy Endpoints

In addition to evaluation of DCR, ORR, DOR and PFS by RECIST 1.1 criteria exploratory endpoints of irDCR, irORR, irDOR and irPFS were planned to be evaluated by irRECIST criteria (Appendix 7 or 8 in the protocols). For studies that did not collect these immune-related responses no analysis will be performed.

8.7.7 Other Exploratory Efficacy Endpoints

Time to initial response (PR or better) in months will be calculated and summarized.

8.7.8 Pharmacokinetic, Pharmacodynamic and Biomarker Analyses

Additional pharmacodynamic, pharmacokinetic and biomarker analyses may be performed, as deemed appropriate. A separate analysis plan for these analyses will be developed by PK/PD group.

8.8 Sensitivity Analyses

Sensitivity analyses will be done using efficacy evaluable analysis set for efficacy endpoints of ORR. if the primary and sensitivity analysis of ORR are consistent, we won't perform sensitivity analysis using efficacy evaluable analysis set for DOR, PFS, and OS. They are also referenced in corresponding parts of section 9.7.

9. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Exploratory endpoints of irDCR, irORR, irDOR and irPFS were planned to be evaluated by irRECIST criteria. For studies that did not collect these endpoints no analysis will be performed. These changes will also be documented in the Clinical Study Report.

Also, one event of clinical interest (ECIs) defined in these protocols (overdose) will not be applicable for this final analysis. Instead, an expanded list of ECIs will be summarized based on the emerging clinical data for acalabrutinib and recent FDA submission in MCL. Overdose, if occurred, will be summarized as part of the important protocol deviations.

10. LITERATURE CITATIONS / REFERENCES

1. Guidance for Industry. Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics. FDA. May 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf

2. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, USDHHS, NIH, NCI; publish date May 28, 2009 (v4.03: June 14, 2010).

3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

4. Bohnsack O, Ludajic K, Hoos A. Adaption of the immune-related response criteria: irRECIST. EMSO 2014, Abstract 4958.

11. APPENDICES

12.1 Definitions

Study Day

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

Duration of Exposure

The duration of exposure to acalabrutinib or pembrolizumab will be calculated in months as (last dose date - first dose date + 1) / 30.4375. The gaps in treatment will be included. The duration of exposure in days will be used for planned dose calculation.

Total Dose

Total dose received is a sum of all actual doses taken through the treatment duration and will be presented in grams. For scheduled drug administration visits that are skipped the actual dose will be 0.

Average Daily Dose (Acalabrutinib)

Average daily dose is total dose divided by duration of exposure in days.

Average Dose per administration cycle (Pembrolizumab)

Average dose per administration cycle is total dose divided by number of cycles for pembrolizumab study treatment.

Relative Dose Intensity

Relative dose intensity is the ratio of total dose to the protocol-specified total dose through the duration of exposure.

12.2 Imputation Rules for Partial or Missing Dates

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, then date of first dose – 1 will be used. If such imputed date for subsequent anticancer therapies is before date of last dose, then 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 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, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

Every effort will be made to obtain complete dates for deaths. If both month and day are missing for death date or a death date is totally missing, do not impute and censor the subject survival time. If death year and month are available but day is missing, the following algorithm will be used:

- If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.

12.3 Censoring Rules for Progression-free Survival

Situation	PFS1	
	Date of Progression or Censoring	**Outcome**
Progression documented on scheduled visit	Date of scheduled visit	Progression
Progression documented between scheduled visits	Date of unscheduled visit	Progression
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censor
Death before first PD assessment	Date of death	Progression
Death between adequate assessment visits	Date of death	Progression
Death or progression after only one missed visit	Date of death	Progression
Death or progression after 2 or more missed visits	Date of last visit with adequate assessment	Censor
Death or progression after 2 or more missed visits and only baseline tumor assessment available	Date of 1st dose of study drug	Censor
No baseline tumor assessments	Date of 1st dose of study drug	Censor
Baseline tumor assessments only and no evidence of documented PD, treatment discontinuation due to PD or death within no more than one missed visit	Date of 1st dose of study drug	Censor
No progression	Date of last visit with adequate assessment	Censor
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censor
New anticancer treatment started	Date of last visit with adequate assessment	Censor

12.4 Censoring Rules for Overall Survival

Situation	Date Death or Censoring	Outcome
Death at any timepoint	Date of death	Death
Lost to follow-up immediately after 1st dose of study drug	Date of 1st dose study drug	Censored
Not known to have died at or after the analysis cutoff date	The date last known alive before data analysis cutoff	Censored
Known to have died after the analysis cutoff date	Date of data analysis cutoff	Censored

12.5. Events of Clinical Interest for acalabrutinib

The Events of Clinical Interest (ECIs) have been identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib, and pharmacological effects of approved BTK inhibitor. The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by SOC, or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category name	Sub-category name	Definition
Cardiac events		• SOC Cardiac disorders
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Febrile Neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other Leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Cytopenias - Thrombocytopenia		• SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		• SMQ Haemorrhage terms (excl laboratory terms)
	Major hemorrhage	• As per Acerta definition below
Hepatic Events		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions • SMQ [narrow] Liver related investigations signs • SMQ [narrow] Hepatitis, non-infectious
Hypertension		• SMQ Hypertension [narrow]
Infections		• SOC Infections and infestations
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease
Second primary malignancies		• SMQ Malignant or unspecified tumours and SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding skin)	• SMQ Malignant or unspecified tumours and SMQ Myelodysplastic syndrome [narrow], excluding skin (i.e. exclude SMQ Skin neoplasms, malignant and unspecified)
Tumor lysis syndrome		• PT Tumour lysis syndrome

MedDRA version 20.1

Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is serious, or Grade ≥ 3 in severity, or that is a central nervous system (CNS) hemorrhage (any severity grade).

Search Strategy:

I. Use standardized MedDRA v19.1 Query:
   - Haemorrhage terms (excl laboratory terms) (SMQ) [20000039]

II. Identify Major Events that are a subset of the Haemorrhage SMQ:
   - Grade ≥ 3 AE
   - Any SAE
   - All Grades of CNS hemorrhage

CNS hemorrhage Preferred Terms (MedDRA v19.1):

Acute haemorrhagic leukoencephalitis	Haemorrhagic transformation stroke
Basal ganglia haematoma	Intracerebral haematoma evacuation
Basal ganglia haemorrhage	Intracranial haematoma
Basilar artery perforation	Intracranial tumour haemorrhage
Brain contusion	Intraventricular haemorrhage
Brain stem haematoma	Intraventricular haemorrhage neonatal
Brain stem haemorrhage	Meningorrhagia
Brain stem microhaemorrhage	Ocular retrobulbar haemorrhage
Central nervous system haemorrhage	Optic disc haemorrhage
Cerebellar haematoma	Optic nerve sheath haemorrhage
Cerebellar haemorrhage	Periventricular haemorrhage neonatal
Cerebellar microhaemorrhage	Pituitary haemorrhage
Cerebral aneurysm perforation	Putamen haemorrhage
Cerebral aneurysm ruptured syphilitic	Ruptured cerebral aneurysm
Cerebral arteriovenous malformation haemorrhagic	Spinal cord haematoma
Cerebral artery perforation	Spinal cord haemorrhage
Cerebral haematoma	Spinal epidural haematoma
Cerebral haemorrhage	Spinal epidural haemorrhage
Cerebral haemorrhage foetal	Spinal subarachnoid haemorrhage
Cerebral haemorrhage neonatal	Spinal subdural haematoma
Cerebral microhaemorrhage	Spinal subdural haemorrhage
Encephalitis haemorrhagic	Subarachnoid haematoma
Epidural haemorrhage	Subarachnoid haemorrhage
Extradural haematoma	Subarachnoid haemorrhage neonatal
Haemorrhage intracranial	Subdural haematoma
Haemorrhagic cerebral infarction	Subdural haematoma evacuation
Haemorrhagic stroke	Subdural haemorrhage
Subdural haematoma evacuation	Subgaleal haematoma
Subdural haemorrhage	Thalamus haemorrhage
Subdural haemorrhage neonatal	Traumatic intracranial haemorrhage

12.6. Events of Clinical Interest for a combination of acalabrutinib and pembrolizumab

The Events of Clinical Interest (ECIs) for a combination treatment have been identified based on preclinical findings, emerging data from clinical studies, and finding from post marketing (for pembrolizumab).
The AEs selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by SOC, by PT or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

Category name	Sub-category name	Definition
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Febrile Neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other Leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above
Infections		• SOC Infections and infestations
Transaminases elevation		• PT Alanine aminotransferase increased • PT Aspartate aminotransferase increased • PT Transaminases increased
Immune-mediated pneumonitis		• PT Pneumonitis
Immune-mediated colitis		• PT Colitis
Immune-mediated hepatitis		• PT Hepatitis • PT Autoimmune hepatitis
Immune-mediated endocrinopathies - Hypophysitis		• PT Hypophysitis • PT Hypopituitarism • PT Adrenal insufficiency
Immune-mediated endocrinopathies - Thyroid disorders		• PT Hyperthyroidism • PT Hypothyroidism • PT Thyroiditis
Immune-mediated endocrinopathies - Type 1 diabetes		• PT Type 1 diabetes mellitus • PT Diabetic ketoacidosis
Immune-mediated nephritis		• PT Nephritis
Immune-mediated skin adverse reactions		• PT Stevens-Johnson syndrome • PT Toxic epidermal necrolysis

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