Statistical Analysis Plan

NCT Number: NCT04157517

Title: An Open-Label, Dose-Escalation Phase 1b/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Antitumor Activity of Modakafusp Alfa (TAK-573) as a Single Agent and in Combination With Pembrolizumab in Adult Patients With Advanced or Metastatic Solid Tumors

Study Number: TAK-573-1001

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-573-1001

An Open-Label, Dose-Escalation Phase 1b/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Modakafusp Alfa (TAK-573) as a Single Agent and in Combination with Pembrolizumab in Adult Patients With Metastatic Solid Tumors

PHASE 1b/PHASE 2

Version**:** Final 3.0

Date**:** 8 November 2021

Prepared by:

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Based on:

Protocol Version: Amendment 4

Protocol Date: 11 August 2021

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

Approvers:

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1.2 Summary of Changes

Summary of Changes from Version 2 to Version 3 of the SAP		
Location	***Description***	***Rationale***
Title Throughout SAP	Update the drug name from TAK-573 to modakafusp alfa.	Update according to PA4
Section 4.2.2 Secondary Objectives Section 4.2.3 Exploratory Objectives Section 5.2 Secondary Endpoints Section 5.3 Exploratory Endpoints	Downgraded the CD38 receptor occupancy objective and endpoint from secondary to exploratory.	Update according to PA4
Section 4.2.2 Secondary Objectives Section 4.2.3 Exploratory Objectives Section 5.2 Secondary Endpoints Section 5.3 Exploratory Endpoints	Downgraded the Type I interferon gene expression signatures objective and endpoint to exploratory.	Update according to PA4
Section 6.0 Determination of Sample Size Section 7.13 [redacted]	[redacted]	Update according to PA4
Section 6.0 Determination of Sample Size	Corrected "regresson" to "regression".	Correction
Section 7.9 Efficacy Analysis	Added the size value of target lesion when it is too small to measure.	Clarification
Section 7.9 Efficacy Analysis	Added censoring rule for the primary analysis of DoR, PFS and TTP for patients who missed two consecutive disease assessments.	Clarification
Section 7.10.1.2 Serum PK Parameters	Added boxplot as well as regression analysis for PK parameters	Update
Section 7.12.1 Adverse Events	Updated the definition of "on-study deaths"	Update according to PA4
Section 7.12.1 Adverse Events	Added AESIs for both modakafusp alfa and pembrolizumab.	Update according to PA4
Appendix A By-Subject Listing	Added "status of non-target lesion, status of new lesion" for Efficacy.	Update
Appendix B Date Imputation Rules	Delete the imputation rules regarding "ongoing" flag for AE since this variable is not captured in the database.	Update

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC∞	area under the serum concentration-time curve from time 0 to infinity
AUClast	area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration
AUCt	area under the plasma concentration versus time curve from 0 to time t
BLRM	Bayesian Logistic Regression Model
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CD38+	CD38-expressing
cfDNA	cell-free DNA
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum observed serum concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
EWOC	Escalation with Overdose Control
FDA	[United States] Food and Drug Administration
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IFN	Interferon
IFN-α	interferon-alpha
IFN-α 2b	interferon-alpha 2b

Ig	immunoglobulin
IL	Interleukin
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
KD	disassociation constant
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
mRECIST v1.1	modified (or revised) Response Evaluation Criteria in Solid Tumors, Version 1.1
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease; disease progression
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
QTcF	QT interval with Fridericia correction method
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
RP2D	recommended phase 2 dose
SA	single agent
SAE	serious adverse event
SD	stable disease
SOC	standard of care
t1/2z	terminal disposition phase half-life
T4	free thyroxine
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of maximum observed serum modakafusp alfaconcentration
TSH	thyroid-stimulating hormone

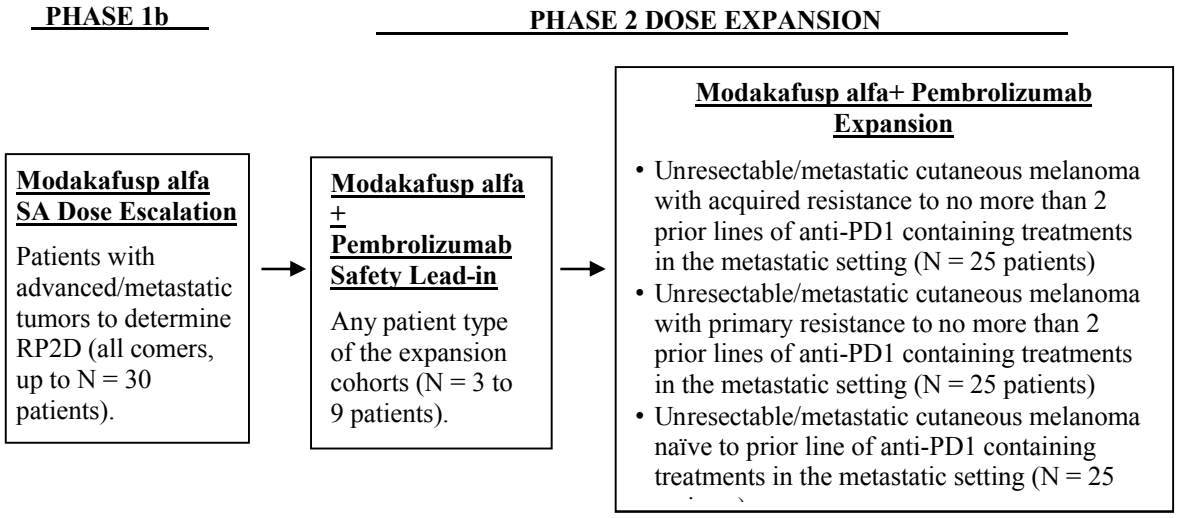
4.0 STUDY DESIGN AND OBJECTIVES

4.1 Study Design

This is an open-label, phase 1b/2 study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and antitumor response of modakafusp alfa as a single agent (SA) and in combination with pembrolizumab in patients with advanced or metastatic solid tumors.

The study consists of 2 phases as shown in Figure 4-a.

Figure 4-a Study Schema



Phase 1b Single-Agent Dose Escalation

Phase 1b will enroll patients with advanced/metastatic solid tumors that have no standard therapeutic option, are intolerant to those therapies, or have refused them.

The modakafusp alfa SA dose escalation phase is designed to determine the single agent recommended phase 2 dose (RP2D) and schedule of modakafusp alfa for further testing. The single-agent RP2D may be either the maximum tolerated dose (MTD) based on dose limiting toxicities (DLTs) or a pharmacologically active dose (PAD) defined by the PK/pharmacodynamic model or exposure-response (ER) analysis in place.

A minimum of 3 patients will be enrolled in the starting dose cohort of modakafusp alfa 0.1 mg/kg administered every 3 weeks (Q3W). Doses will be escalated as follows: 0.1, 0.2, 0.4, 0.75, 1.5, 3 and 6 mg/kg. Patients will be assessed for DLTs until Cycle 2 Day 1 (C2D1) can be

administered from a safety standpoint. If there are no DLTs in the first cohort of 3 evaluable patients dosed at 0.1 mg/kg, Bayesian Logistic Regression Model (BLRM) guided by the Escalation with Overdose Control (EWOC) principle will be used in successive dose escalation cohorts to estimate the next dose level.

Phase 2 Dose Expansion

Enrollment into phase 2 expansion in combination with pembrolizumab will be initiated once the RP2D of modakafusp alfa single agent has been determined in phase 1b.

The combination treatment cohorts will begin with a single safety-lead in period to evaluate safety and tolerability during the Cycle 1 DLT evaluation period of modakafusp alfa in combination with pembrolizumab. If there are no DLTs in the first 3 patients during Cycle 1 of the safety lead-in period with modakafusp alfa SA RP2D in combination with pembrolizumab 400 mg every 6 weeks (Q6W), the combination dose and regimen could be selected for the 3 disease cohorts described below. If there is 1 DLT in the initial 3 patients in the safety-lead in period, an additional 3 patients will be enrolled at the same modakafusp alfa RP2D in combination with pembrolizumab 400 mg Q6W. If there are ≥2 DLTs in the first 3 patients at the modakafusp alfa SA RP2D, enrollment will resume at the next lower dose level of modakafusp alfa RP2D in combination with pembrolizumab. Other approved pembrolizumab dosing regimens (e.g., 200 mg Q3W) could be tested in the safety-lead in period if 400 mg Q6W in combination with modakafusp alfa at one dose lower than RP2D is intolerable.

For the safety lead-in period, patient enrollment will be staggered between the first and second patients by 7 days. The second and third patients can be dosed concurrently if the first patient in the cohort has gone through the Day 8 visit without clinically significant acute toxicities. Patients enrolled in the safety lead-in phase could have any of the 3 melanoma disease categories described below.

Following completion of the safety lead-in phase and review of safety data, phase 2 of the study will further explore the safety and efficacy of modakafusp alfa treatment in combination with pembrolizumab. The combination cohorts, including patients in the safety-lead phase, will enroll patients with unresectable/metastatic melanoma in the following subgroups:

I. Unresectable/metastatic cutaneous melanoma with primary resistance to no more than 2 prior lines of anti-PD1 containing treatments in the metastatic setting.
II. Unresectable/metastatic cutaneous melanoma with acquired resistance to no more than 2 prior lines of anti-PD1 containing treatments in the metastatic setting.

III. Unresectable/metastatic cutaneous melanoma naïve to prior anti-PD1 containing treatments in the metastatic setting.

If modakafusp alfa in combination with pembrolizumab is safe and meaningful clinical activity is seen, additional expansion cohorts may be added to assess other tumor types.

4.2 Objectives

4.2.1 Primary Objectives

The primary objective is to determine the safety and tolerability of modakafusp alfa as SA in patients with locally advanced or metastatic solid tumors (phase 1b) and in combination with pembrolizumab in unresectable/metastatic cutaneous melanoma (phase 2 safety lead-in) and to evaluate the efficacy of modakafusp alfa in combination with pembrolizumab in patients with unresectable/metastatic cutaneous melanoma (phase 2 expansion).

4.2.2 Secondary Objectives

The secondary objectives are:

- To define the MTD and/or the PAD of modakafusp alfa SA, if applicable (phase 1b).
- To select the RP2D of modakafusp alfa SA (phase 1b) and in combination with pembrolizumab (phase 2 safety lead-in).
- To evaluate modakafusp alfa PK as a SA (phase 1b) in combination with pembrolizumab (phase 2 safety lead-in).
- To assess the preliminary antitumor activity of modakafusp alfa as a SA (phase 1b).
- To further characterize the antitumor effect of modakafusp alfa in combination with pembrolizumab based on immune Response Evaluation Criteria in Solid Tumors (iRECIST) in expansion cohort patients (phase 2 expansion)
- To evaluate safety and tolerability of modakafusp alfa in combination with pembrolizumab (phase 2 expansion).
- To characterize the immunogenicity of modakafusp alfa in patients with solid tumors (phase 1b and phase 2).

4.2.3 Exploratory Objectives

The exploratory/additional objectives are:

- To assess modakafusp alfa CD38 receptor occupancy (RO) of peripheral immune cells in patients treated with modakafusp alfa as a SA (phase 1b) or in combination with pembrolizumab (phase 2).
- To explore predictive biomarkers of response (phase 1b and phase 2).
- To evaluate the effect of modakafusp alfa on QTcF intervals (phase 1b and phase 2 safety lead-in).
- To evaluate the relationship between administered dose and exposure of modakafusp alfa, RO of CD38, and IFN pathway induction as evaluated by gene expression changes and production of cytokines/chemokines (phase 1b and phase 2).
- To evaluate the relationship between evidence of IFN pathway induction with evidence of activation of the innate and/or adaptive immune response as assessed by changes in immunophenotype and T-cell antigen receptor (TCR) clonality of peripheral blood and tumor (phase 1b and phase 2).
- To evaluate the relationship between modakafusp alfa exposure and/or CD38 RO with immune cell activation (as described above), and clinical response (phase 1b and phase 2).
- To evaluate correlations between baseline tumor IFN pathway gene expression with either the degree of IFN pathway induction or the level of immune cell activation on treatment (phase 1b and phase 2).
- To characterize germline DNA variants for correlations with clinical outcome, pharmacodynamic effects, and PK (phase 1b and phase 2).
- To further characterize the antitumor effect of modakafusp alfa based on changes in the tumor growth rate between the most immediate pretreatment period and on treatment (phase 1b and phase 2).
- To characterize serum PK of pembrolizumab when administered in combination with modakafusp alfa (phase 2).
- To assess the Type I interferon (IFN) gene expression signature in peripheral blood (phase 1b and phase 2).
- To evaluate correlations with clinical outcome with either the on-treatment immunophenotype of the tumor microenvironment or changes in the immunophenotype from baseline (phase 2).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are:

- Frequency and severity of treatment-emergent adverse events (TEAE) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 (phase 1b and phase 2 safety lead-in).
- Number of patients with DLTs (phase 1b and phase 2 safety lead-in).
- Number/percentage of patients with 1 or more SAEs (phase 1b and phase 2 safety lead-in).
- Number/percentage of patients with 1 or more TEAE leading to dose modification and/or treatment discontinuation (phase 1b and phase 2 safety lead-in).
- Overall response rate (ORR) (complete response [CR] + partial response [PR]) assessed according to modified Response Evaluation Criteria in Solid Tumors, Version 1.1 (mRECIST v1.1) for melanoma patients (phase 2 expansion).

5.2 Secondary Endpoints

The secondary endpoints are:

- MTD or PAD (as defined in Section 6.1.1 of Protocol Amendment 4), if available (phase 1b).
- RP2D for SA and in combination with pembrolizumab, respectively (phase 1b and phase 2 safety lead-in).
- Frequency and severity of TEAEs according to the NCI CTCAE v.5 (phase 2 expansion).
- Number/percentage of patients with 1 or more SAEs (phase 2 expansion).
- Number/percentage of patients with 1 or more TEAE leading to dose modification and/or treatment discontinuation (phase 2 expansion).
- PK parameters after the first dose of modakafusp alfa on Cycle 1 Day 1 (C1D1) and on Cycle 2 Day 1 (C2D1) for dose escalation phase (phase 1b) and on Cycle 1 Day 1 (C1D1) and Cycle 3 Day 1 (C3D1) for the phase 2 safety lead-in phase of dose expansion, including but not limited to:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the plasma concentration versus time curve from time 0 to time t (AUC_t).
  - Area under the concentration-time curve from time 0 to infinity (AUC_∞).
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Clearance.

  - Volume of distribution at steady state (V_{ss}).
- Overall response rate (ORR) (complete response [CR] + partial response [PR]) assessed according to the mRECIST v1.1 for patients in dose escalation (phase 1b).
- Disease control rate (DCR) (CR + PR + stable disease [SD]) (phase 1b and phase 2).
- Duration of response (DOR) (phase 1b and phase 2).
- Time to progression (TTP) (phase 1b and phase 2).
- Progression-free survival (PFS) assessed according to mRECIST v1.1 (phase 1b and phase 2).
- Overall survival (OS) (phase 1b and phase 2).
- Efficacy measures of ORR, DCR, DOR, TTP, and PFS based on iRECIST (phase 2 expansion)
- Anti–modakafusp alfa antibody incidence and titer (phase 1b and phase 2).

Definitions and timeframes of primary and secondary endpoints are provided in protocol Section 6.3.3.

5.3 Exploratory Endpoints

The exploratory endpoints are:

- Tumor mutations characterized from cell-free DNA (cfDNA) and quantification of circulating tumor cells (CTCs) will be evaluated at baseline and assessed for correlations with clinical response.
- Genomic and protein expression of baseline tumor tissue
- Germline mutations and polymorphisms as assessed by whole exome sequencing of peripheral blood
- Change of QTcF interval using data from PK time matched triplicated electrocardiogram (ECG) readings.
- Induction of modakafusp alfa–induced gene expression changes, including type I IFN signature, assessed in peripheral blood and tumor.
- Fold-change in plasma levels of IP-10 and other cytokines/chemokines.
- Immune cell activation as assessed in peripheral blood and tumor by: (a) immunophenotypic changes and (b) evaluation of TCR diversity.
- Modakafusp alfa antitumor effect size based on observed change in tumor growth rate using prescreening, screening, and on-treatment diagnostic imaging, as available.
- Serum PK of pembrolizumab when administered in combination with modakafusp alfa.

- Cellular CD38 RO of peripheral blood assessed at time points surrounding the first and second modakafusp alfa SA administrations (phase 1b) and at time points surrounding the first and third modakafusp alfa administrations when in combination with pembrolizumab (phase 2).
- Modakafusp alfa-induced Type I IFN gene expression signature in the peripheral blood (phase 1b and phase 2).
- Immunophenotypic evaluations of the tumor and tumor microenvironment utilizing multiplexed immunohistochemistry or similar methodologies.

6.0 DETERMINATION OF SAMPLE SIZE

Phase 1 Dose escalation

It is expected to enroll approximately 30 patients. A minimum of 3 patients will be enrolled in the starting dose level. Starting from the second dose level, an adaptive Bayesian Logistic Regression Model (BLRM) guided by the Escalation With Over-Dose Control (EWOC) principle will be used for all subsequent dose escalation recommendations.

Phase 2 Dose expansion

The study will enroll up to 25 patients in each phase 2 dose expansion disease subgroup. A Bayesian predictive probability design will be used to allow multiple futility analyses to stop early for futility. Enrollment into phase 2 will be initiated once the RP2D of modakafusp alfa has been determined in phase 1b of the study.

The combination treatment cohorts will begin with a single safety-lead in period during which 3 to 9 patients will be evaluated for safety and tolerability during their first cycle of modakafusp alfa with pembrolizumab.

Up to 25 patients will be enrolled in each of the 3 disease subgroup cohorts. Assuming 3 to 9 safety lead-in patients, the total sample size for phase 2 can be up to 84 patients.

[redacted]

[redacted]

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 MTD Estimation

The 2-parameter BLRM implementing the EWOC principle (Babb et. al. 1997, Neuenschwander et. al. 2008) will be used to inform dose escalation decisions and MTD estimation starting from the second dose cohort. The final decision on next dose level will be taken jointly by the sponsor and the participating investigators.
BLRM with overdose control (Appendix C) will be used to inform dose escalation decisions and MTD estimation, along with consideration of other emerging safety, clinical, PK, and pharmacodynamic data.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics. The initial size of each cohort will be approximately 3 evaluable patients.
Initially, 3 patients will be enrolled at the 0.1 mg/kg starting dose level. The following rules will be used only for this initial cohort:

- If none of the 3 patients experiences a DLT during the first cycle, the dose may be escalated to the next planned dose level.
- If 1 of the 3 patients exhibits a DLT, then the cohort will be expanded from 3 patients to a total of 6 patients.
  - If no more than 1 patient out of the 6 total patients has a Cycle 1 DLT, 3 patients will be enrolled at the next dose level.
  - If 2 of the 6 patients have a Cycle 1 DLT, 3 additional patients will be enrolled. If any of the 3 additional patients have a Cycle 1 DLT, the starting dose will be considered not tolerated and the dose will be de-escalated to 0.05 mg/kg. If none of the 3 additional patients have a Cycle 1 DLT, the starting dose may be considered the MTD or may be escalated to the next dose level, after consideration of other available safety, clinical, PK, and pharmacodynamic data.

  - If 3 or more of the 6 patients experience a Cycle 1 DLT, the starting dose level will be considered not tolerated and the dose will be de-escalated 0.05 mg/kg following review of all available safety data and approval of the sponsor.
- If 2 or more of the 3 patients experience a DLT, then the starting dose level will be considered too toxic and the dose will be de-escalated to 0.05 mg/kg.

Starting from the second dose level, the BLRM with overdose control will be used for all subsequent dose escalation recommendations. The BLRM recommended dose at the end of each dosing cohort will be that which has the highest posterior probability of having a DLT rate that is ≥0.16 and ≤0.33. Following the EWOC principle, the posterior probability of the recommended dose having a DLT rate above 0.33 must not exceed 35%. Escalation will continue until one of the following stopping rules is met before reaching the maximum number of patients:

- At least 6 patients are enrolled at the current dose, the current dose is the BLRM recommended dose for the next group of patients, and the observed DLT rate is ≤33%, OR
- If the next recommended dose is a tested dose and has already enrolled 9 patients, the BLRM posterior probability of the next recommended dose having a DLT rate that falls into the interval [0.16, 0.33) exceeds 50%, and the observed DLT rate is ≤33%.

Once either of the above rules has been met, MTD may be declared. Alternative stopping rules may also be considered following discussions between the sponsor and the investigators.

The description and operating characteristics of the BLRM for dose escalation are included in Appendix C.

Posterior probability of under-toxicity [0,0.16), target toxicity [0.16,0.13), and over-toxicity [0.33,1] will be summarized in the CSR based on all the data in the dose escalation phase for patients in DLT-evaluable set.

7.2 General Principles

All statistical analyses will be conducted using SAS® Version 9.4 (SAS Institute, Cary, NC).

For categorical variables, the count and proportions of each possible category value will be tabulated. The denominator for the proportion will be based on the number of subjects in the analysis sets. For continuous variables, the mean, median, SD, minimum, and maximum values will be presented for all patients in the relevant analysis set.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Minimum and maximum are presented using the same number of decimal places as the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided. P-values should be presented to 3 decimal places, with values less than 0.001 presented as <0.001.

Baseline values are defined as the last observed value before the first dose of the study drug.

The summary tables will include escalation cohorts, overall for dose escalation phase, safety lead-in cohort in expansion phase, and by expansion cohorts and overall for expansion phase and overall for both phases as appropriate.

7.2.1 Data Presentations

Modakafusp alfa Single Agent Dose Escalation: by dose level

Dose Level 1	Dose Level 2	Dose Level 3	Continue for each dose level	Total escalation

Modakafusp alfa + Pembrolizumab Safety Lead-in: by dose level

Safety Lead-in Dose Level 1	Safety Lead-in Dose Level 2	Continue for each dose level	Total Safety Lead-in

Modakafusp alfa + Pembrolizumab Dose Expansion: by cohort

Cohort I (Primary Resistance)	Cohort II (Acquired resistance)	Cohort III (Naïve to Prior Anti-PD1)	Total expansion

Total: total escalation, total safety lead-in, total expansion, total population

Total escalation	Total safety lead-in	Total expansion	Total

7.2.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug (excluding test dose if any). Other study days are defined relative to the study Day 1 and the study Day -1 (the day prior to Study Day 1).

7.2.3 Methods for Handling Missing Data

For efficacy and safety data, no imputation of values for missing data will be performed. Imputation rules for incomplete dates are described in Appendix B.

7.3 Analysis Sets

- Safety Analysis Set: The safety analysis set will include all enrolled patients who received at least one dose (even incomplete) of the study drug.
- Response evaluable Analysis set: The response evaluable analysis set is a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 post-treatment evaluation.
- DLT Evaluable Analysis Set: patients who receive all Cycle 1 doses of modakafusp alfa or experience a DLT in Cycle 1 in the dose-escalation portion of the study; or patients who or receive all Cycle 1 doses of modakafusp alfa in combination with pembrolizumab or experience a DLT in Cycle 1 in the safety lead-in portion of the study.
- Pharmacokinetic Analysis Set: patients from the safety analysis set who have sufficient data to calculate at least 1 PK parameter for modakafusp alfa.
- Immunogenicity-evaluable Analysis Set: Includes patients with a baseline and at least one post-baseline immunogenicity assessment.

7.4 Disposition of Subjects

Study information, including the date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, MedDRA Version, WHO Drug Version, and SAS Version is presented. For screen failure patients, who signed informed consent and were not treated in the study, demographics and the reasons for screen failures will be generated in a summary table.

The disposition includes the number and percentage of patients in the following categories: patients in each of the study populations, primary reason off treatment, ongoing (if applicable at the time of database lock/data cut-off), participating in PFS follow-up, and the primary reason discontinued from the study. This information will be presented by safety analysis set.

7.5 Demographic and Other Baseline Characteristics

All demographics and baseline characteristics will be summarized by safety analysis set.

Demographics

Demographic data to be evaluated will include age, sex, race, ethnicity, height, and weight.

Disease characteristics:

- Type of cancer
- Years since initial diagnosis [(date of the first dose – date of the diagnosis) / 365.25)].
- Anatomic stage

- Number of sites of cancer involvement
- Eastern Cooperative Oncology Group (ECOG) performance status.

Prior therapy

- Prior radiation.
- Prior surgery/procedure.
- Prior systemic anti-cancer therapy.
- Lines of prior therapy (descriptive statistics and categorical summary: 0, 1, 2, 3, 4, 5, 6, >6).
- Lines of prior therapy initiated within 12 months of the first dose of the study drug (categorical summary).
- Last line of prior therapy
- Best response at the last line of therapy

7.6 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the latest MedDRA dictionary. Concurrent medical conditions are the ones ongoing or started on or after the day inform consent was signed. Medical history and concurrent medical conditions will be summarized separately by safety analysis set. Medical history and concurrent medical conditions will be listed together along with a flag about whether the medical condition is concurrent or not. If both start date and stop date are missing, medical condition will be assumed to start before inform consent and continue after treatment discontinuation. If only start date is missing, then medical condition will be assumed to start before inform consent. If stop date is missing, then medical condition will be assumed to continue after treatment discontinuation.

7.7 Medication History and Concomitant Medications

Medication history and Concomitant medications will be coded using the latest World Health Organization (WHO) Drug Dictionary. Concomitant medication is defined as the medication ongoing or started on or after the first dose date of the study drug through 30 days after the last dose of the study drug, or the start of subsequent anti-cancer therapy, whichever occurs first. The number and percentage of patients taking concomitant medications will be tabulated by WHO standardized medication name. Medication history will also be summarized. Medication history and concomitant medication will be listed together with the following flags:

1. Discontinued before the first dose date of the study drug.
2. Started on or after dosing.

3. Started after 30 days after the last dose of the study drug, or the start of subsequent anti-cancer therapy, whichever occurs first.

If both start date and stop date are missing, medication will be assumed to start before the first dose date of the study drug and continue after treatment discontinuation. If only start date is missing, then medication will be assumed to start before the first dose date of the study drug. If only stop date is missing, then medication will be assumed to continue after treatment discontinuation.

7.8 Study Drug Exposure and Compliance

Extent of Exposure

The exposure to study drugs (modakafusp alfa and Pembrolizumab) will be characterized by summaries and descriptive statistics of duration of treatment in weeks, number of treated cycles (1, 2, 3, 4, 5, 6, 7-12, >12 and summary statistics), and relative dose intensity will be summarized by safety analysis set.

A treated cycle is defined as a cycle in which any amount of the study drug for at least one of the dosing days in the cycle is given.

Cumulative dose (mg/kg): sum of all doses of the study drug administered to a subject during the treatment period.

Relative dose intensity = (actual dose per week / planned dose per week) × 100. The actual dose per week adjusts for delays in the start of a cycle and assumes the last cycle is fixed at the intended duration.

- Date of last exposure of the study drug=min(date of last dose of the study drug + treatment interval-1, date of death, start date of the subsequent treatment-1). This algorithm may be adjusted as appropriate by consulting the study clinician.

Actual dose per week and planned dose per week are calculated as follows:

- Actual dose per week: cumulative dose of the study drug in mg/kg / [(date of the last exposure of the study drug – date of the first dose+1) /7].
- Planned dose per week: starting dose of study drug (mg/kg) on C1D1 / treatment interval in weeks.

Action on Study Drug

The reason for dose modification (increased, reduced, interrupted, withdrawn, delayed, drug infusion interrupted, infusion rate increased, infusion rate reduced) of the study drug will be summarized by cycle for the safety analysis set.

7.9 Efficacy Analysis

Response will be assessed according to mRECIST 1.1 for all patients. Response will also be assessed according to iRECIST for patients in Phase 2 expansion cohort.

Best Overall Response (BOR)

Best overall response is defined as the best response (per investigator assessment as defined by mRECIST 1.1 or iRECIST Criteria) recorded after the first dose of the study drug until a subsequent anti-cancer therapy. Response assessments after treatment discontinuation but before the initiation of a subsequent anti-cancer therapy should be included in the analysis of BOR. This will be ordered from best to worst: Complete Response (CR or iCR), Partial Response (PR or iPR), Stable Disease (SD or iSD), Progressive Disease (PD, iUPD or iCPD), Not Evaluable (NE or iNE).

Waterfall plots for best percentage change in the size of target lesions as per mRECIST 1.1 criteria will also be presented. The plot will have the following information:

1. Response,
2. Dose,
3. Cohort
4. Phase (escalation, safety lead-in or expansion).

Best overall response will be summarized and listed for all patients in the response evaluable analysis set. Overall response will be listed for all patients in the response evaluable set for each visit along with percentage change in the size of target lesions per mRECIST 1.1 criteria. If target lesion is believed to be present but too small to measure, a value of 5 mm is assigned per mRECIST 1.1.

Overall Response Rate (ORR)

The ORR is defined as the proportion of patients who have achieved the best response of CR or PR during the study per investigator assessment as defined by mRECIST 1.1 or iRECIST Criteria. The ORR will be summarized by frequencies and percentages for patients in the response evaluable analysis set. A binomial exact confidence interval will also be provided when possible.

Disease Control Rate (DCR)

The DCR is defined as the proportion of patients who have achieved the best response of CR, PR or SD during the study per investigator assessment as defined by mRECIST 1.1 or iRECIST Criteria. The DCR will be summarized by frequencies and percentages for patients in the response evaluable analysis set. A binomial exact confidence interval will also be provided when possible.

Duration of Response (DOR)

The DOR will be tabulated for those patients with a CR or PR during the study per investigator assessment as defined by mRECIST 1.1 or iRECIST Criteria in the response evaluable analysis set with a reasonable number of responses. The DOR is defined as the number of days from the first documentation of a response until progressive disease or death, whichever occurs first. If a patient misses two consecutive disease assessments, then follow-up for the primary endpoint will be censored at the time of last non-progressive scan prior to the missed interval.

The censoring rules and censoring date in the analysis of DOR will be the same as for PFS and TTP.

DOR (months) = (date of progression or death or censor – date of confirmed response + 1)/30.4375.

The Kaplan-Meier method will be used to estimate the distribution of DOR. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method (Brookmeyer and Crowley 1982), will be presented. The number of patients with events and the number of patients censored will be summarized. DOR for all patients with a response will be listed.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose to the date of PD (or iCPD) (per investigator assessment as defined by mRECIST 1.1 or iRECIST Criteria) or the date of death due to any cause, whichever occurs first. Patients without documentation of PD (or iCPD) or death will be censored at the date of the last response assessment that is SD (iSD) or better, and prior to or on the date of initiation of alternative anti-cancer therapy if patients start new treatments. Patients with no post baseline response assessment will be censored on day 1.

PFS (months) = (earliest date of progression or death or censor – date of first dose + 1)/30.4375.

The analysis of PFS will be based on the safety analysis set with a reasonable number of patients. The Kaplan-Meier method will be used to estimate the distribution of PFS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier PFS

probability estimates with 95% CIs at 3 and 6 months (or later time points if data permits) will be presented. The number of patients with events along with the type of events (death or progressive disease) and the number of patients censored will be summarized.
PFS for all patients in the safety analysis set will be listed.

Overall Survival (OS)

Overall survival in months is defined as the time from the date of first dose to the date of death of any cause [OS (months) = (date of death or censor – date of first dose + 1)/30.4375)]. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.
The analysis of OS will be based on the safety analysis set with a reasonable number of patients. The Kaplan-Meier method will be used to analyze the distribution of OS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier estimates with 95% CIs at 6 and 12 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.
OS for all patients in the safety analysis set will be listed.

Time to Progression (TTP)

Time to progression is defined as the time from first dose to the date of first documentation of objective progression. Patients without documentation of PD (iCPD) will be censored at the date of the last response assessment that is SD or better prior to the date of initiation of alternative anti-cancer therapy. Patients with no post baseline response assessment will be censored on day 1.
TTP (months)= (date of progression or censor – date of first dose + 1)/30.4375).
The Kaplan-Meier method will be used to estimate the distribution of TTP with a reasonable number of patients in the response evaluable set. Kaplan-Meier curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley, and Kaplan-Meier estimates with 95% CIs at 3 and 6 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis

7.10.1.1 Serum modakafusp alfa Concentrations

Blood samples will be collected at prespecified time points as described in the study protocol for the measurement of serum modakafusp alfa concentrations. Individual serum concentration data will be listed by patient, dose level, study day, and sampling time. Both nominal (scheduled) and actual sampling times will be presented in the listings.

Serum modakafusp alfa concentrations will be summarized by nominal time post dose, grouped by dose level, and study day by phases (escalation and expansion). Summary statistics will be reported at nominal sampling times with at least 2 patients in the PK evaluable population; means will be reported if the number of observations above the lower limit of quantitation (NALQ) is ≥50% of the number of patients. The summary statistics will consist of: N, NALQ, arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, CV of geometric mean, median, min, and max. Arithmetic mean, geometric mean, median, min, and max will be reported on at least 2 non-missing values, while the SD and CV will be reported on at least 3 non-missing values. modakafusp alfa concentrations that are below the limit of quantitation (BLQ) will be set to zero for calculation of summary statistics, except for geometric means, where BLQ values will be considered missing.

Concentration data that are considered anomalous may be excluded from the concentration summaries and plots. Evidence or explanations will be provided in the clinical study report to justify the exclusion of concentration data.

Mean and individual serum modakafusp alfa concentration data will be plotted over nominal sampling time, grouped by dose level, and study day on both linear and semi-logarithmic scales. BLQ values will be plotted as zero on a linear scale and treated as missing on a semi-logarithmic scale.

7.10.1.2 Serum PK Parameters

The serum PK concentration-time course data will be used to calculate standard PK parameters using noncompartmental methods with Phoenix WinNonlin.

Actual sampling times will be used for the calculation of PK parameters. In the event that actual collection times are either unreliable or missing, nominal collection times will be used. For the calculation of PK parameters, serum concentrations of modakafusp alfa that are BLQ will be treated as zero prior to t_{max}, missing between t_{max} and the time of the last measurable concentration, and the concentration-time curve will be considered to have terminated at the time

of the last measurable concentration. If measurable concentrations are near the lower limit of quantification (LLOQ) or imbedded between BLQ concentrations, these values may be excluded at the discretion of the Clinical Pharmacologist. Concentration data that are considered anomalous may not be used in the calculation of PK parameters; evidence or explanations will be provided in the clinical study report to justify the exclusion of data.

The PK parameters including but not limited to the parameters listed below will be determined, as permitted by data:

- C_{max}.
- t_{max}.
- AUC_{∞}.
- AUC_{last}.
- λ_z.
- $t_{1/2z}$.
- CL.
- V_{ss}.
- Accumulation ratio based on AUC_{τ}.

Individual PK parameters will be presented in listings PK parameters, and will be summarized and grouped by dose level, and study day for patients in the Cycle 1 Day 1 (C1D1) and on Cycle 2 Day1 (C2D1) for dose escalation phase (phase 1b) and on Cycle 1 Day 1 (C1D1) and Cycle 3 Day 1 (C3D1) for the phase 2 safety lead-in phase of dose expansion. Arithmetic mean, geometric mean, median, min, and max will be reported on at least 2 non-missing values, while the SD and CV will be reported on at least 3 non-missing values. Except for t_{max}, the summary statistics will consist of: N, mean, SD, CV, geometric mean, CV of geometric mean, median, min, and max. The summary statistics for t_{max} will consist of: N, median, min, and max.

In addition, box plots will be generated for Cmax versus dose and AUC versus dose for Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) for dose escalation phase (phase 1b) and Cycle 1 Day 1 (C1D1) and Cycle 3 Day 1 (C3D1) for the phase 2 safety lead-in phase of dose expansion.

Dose proportionality of the PK of TAK-573 will be evaluated by visual inspection of plots of individual PK parameter values versus dose. If data permit, regression analysis using a power model will also be used to assess dose proportionality.

The PK data collected in this study are intended to contribute to future population PK analyses of modakafusp alfa. These population PK analyses may include data collected in other modakafusp alfa clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will not be reported in the clinical study report.

7.10.2 PK/QTc Analysis

The PK-time matched triplicate ECG data collected in each patient during the dose escalation phase will be pooled to understand the PK-QTc interval relationship of modakafusp alfa. The relationship between modakafusp alfa serum concentration and effects on heart rate and QTcF interval will be analyzed using proper modeling. These population PK-QTc interval analyses may include data collected in other modakafusp alfa clinical studies. As such, the analysis plan for the population PK-QTc interval analysis will be separately defined, and the results of these analyses will be reported separately and not presented in the clinical study report for this study.

7.10.3 Pharmacodynamic Analysis

During the clinical development of modakafusp alfa, several biomarkers will be assessed to test for their correlation with safety and efficacy, if possible. Markers that will be studied are markers linked either to the drug itself or to the treated disease.

Attempts will be made to evaluate potential relationships between both modakafusp alfa dose and modakafusp alfa serum exposure versus safety and efficacy data. These analyses will be exploratory in nature.

A pharmacodynamic analysis will be included in CSR only if there is a trend.

7.11 Other Outcomes

7.11.1 Immunogenicity Analysis

The immunogenicity of modakafusp alfa will be assessed by determining anti–modakafusp alfa antibody incidence and characteristics (e.g., titer and specificity). All ADA data will be listed. For patients in the immunogenicity evaluable analysis set, percent of patients with positive ADA at each timepoint, as well as percent of patients with positive ADA by domain specific assay and ADA titers, will be summarized by dose levels by study phases (escalation and expansion). Percent of patients with positive ADA at baseline and at any post-baseline time point during the study will be reported. Additional summary tables and figures may be generated to assess the impact of anti–modakafusp alfa antibodies on the pharmacokinetic profile, drug efficacy, pharmacodynamic profile, and clinical safety will be evaluated, if possible. These analyses will be exploratory in nature and may be included in CSR if there is a trend.

7.12 Safety Analysis

7.12.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later (based on version at time of database lock). Treatment-emergent is defined as any AE that occurs on or after the date of the first dose of any study treatment through 30 days after the last dose of any study treatment.

Treatment-emergent AEs will be summarized by MedDRA system organ class (SOC), and preferred term. For summary tabulations the following hematologic abnormalities coded to MedDRA preferred terms in the Investigations SOC will be pooled with the appropriate clinical terms in the blood and lymphatic system disorders SOC:

MedDRA Preferred Term (Investigation SOC)	**Mapped to (Blood and lymphatic system disorders SOC)**
Neutrophil count decreased	Neutropenia
Platelet count decreased	Thrombocytopenia
Hemoglobin decreased	Anemia
While blood cell count decreased	Leukopenia

Treatment-emergent AEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Summary tabulations will include the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- Grade 3 and Grade 4 TEAEs (based on maximum severity).
- Grade 3 and Grade 4 drug-related TEAEs (based on maximum severity).
- The most commonly reported treatment-emergent AEs (i.e., those events reported by >= 10% of all patients in each phase or overall population as appropriate).
- Serious treatment-emergent AEs.
- Drug-related serious treatment-emergent AEs.
- Treatment-emergent AEs resulting in discontinuation of study drug.
- Treatment-emergent AEs resulting in study drug modifications (including discontinuation, delay, reduction, and interruption).

- Treatment-emergent AEs resulting in dose delays.
- Treatment-emergent AEs resulting in dose reductions.
- Treatment-emergent AEs resulting in dose interruptions.
- TEAEs leading to death
- Treatment emergent AESI – all grades
- Treatment emergent AESI grade 3 and above
- Treatment emergent AESI grade 3 or 4
- Treatment-emergent AEs resulting in infusion rate reductions.
- Treatment-emergent AEs resulting in infusion interruptions.
- Serious treatment emergent AESI

All summaries will be by dose levels by phases (escalation, safety lead-in, and expansion) for patients in the safety analysis set.

Patients with the same AE more than once will have that event counted only once within each body system, and once within each preferred term. Patients with the same AE more than once will have the maximum intensity of that event counted once within each body system, and once within each preferred term.

Most commonly reported (at least 10% of all patients in each phase or overall population as appropriate) treatment-emergent AEs will be presented by preferred term only. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary TEAE table will include numbers and percentages of patients who had any TEAE, and qualified TEAEs: drug-related AE, not drug-related AE, grade 3 or higher TEAE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, not drug-related SAE, SAEs leading to study drug discontinuation, AEs resulting in study drug discontinuation, and on-study deaths. On-study death is defined as deaths that occur between the first dose of study drug and up to 30 days after the last dose of study drug and deaths assessed related to study drug that occur 30 days after the last dose of study drug.

Most frequent, >5% of all patients in each phase or overall population as appropriate, non-serious TEAE will be presented by system organ class and preferred terms for clinical trial disclosure.

A by-patient listing of DLTs that occur during Cycle 1 of treatment will be presented by dose levels for all patients in the DLT evaluable set. Patients will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

A by-patient listing of all deaths regardless of whether on study or not will also be presented. In this listing, on-study deaths will be flagged.

Adverse Events of Special Interest (AESI)

For modakafusp alfa, infusion-related reactions (IRRs) are designated as AESIs.

For pembrolizumab, the following AEs are considered AESIs:

- Pneumonitis.
- Hepatitis.
- Colitis.
- Nephritis.
- Dermatologic reactions.
- Myocarditis.
- IRR.
- Endocrinopathies, including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and hypophysitis.

7.12.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used. Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will be presented. Scheduled laboratory along with unscheduled lab test results will be listed.

Lab parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, activated partial thromboplastin time (aPTT), platelet count, white blood cell (WBC) count, WBC differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), prothrombin time (PT)
- Chemistry: albumin, alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen, calcium, chloride, creatinine, glucose (non-fasting), HCO_3 or CO_2, LDH, phosphate, potassium, sodium, standard C-reactive protein, urate or uric acid

- Urinalysis: protein, glucose, nitrite, occult blood, specific gravity, pH, bilirubin, ketones, turbidity and color, leukocytes, urobilinogen
- Immunosafety markers: thyroid-stimulating hormone (TSH), free thyroxine (T4), cortisol (morning preferred)

If GFR is to be estimated, the MDRD or CKD-EPI equations shall be used. References are specified in Section 9.3.13.1 of Protocol Amendment 3.

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 5.0 or higher. Shift tables from baseline to the worst values will be constructed for laboratory parameters. Individual platelet and absolute neutrophil count (ANC) profiles will be generated for each dose level. Mean values over time for platelets and ANC will be produced for each phase as appropriate.

7.12.3 Vital Signs

Descriptive statistics for vital sign results (diastolic and systolic blood pressure, heart rate, pulse rate and body weight) will be summarized as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

For blood pressure values collected during the infusion (every 30 minutes), the number and percentage of patients with changes from pre-infusion blood pressure values will be summarized in the following categories:

- Increase of diastolic blood pressure of at least 10 mm Hg during any infusion.
- Decrease of diastolic blood pressure of at least 10 mm Hg during any infusion.
- Increase of systolic blood pressure of at least 20 mm Hg during any infusion.
- Decrease of systolic blood pressure of at least 20 mm Hg during any infusion.

7.12.4 12-Lead ECGs

ECG data (ventricular rate, RR interval, PR interval, QT interval, and QTcF interval) will be summarized as follows:

- Baseline value (C1D1 or screening if C1D1 is not available).
- Minimum post-baseline value.
- Change to Minimum post-baseline value.
- Maximum post-baseline value.
- Change to Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (<450 msec, 450-480 msec, >480-<500 msec, and ≥500msec) will be summarized at baseline and each of the subsequent time points. Categories of changes from baseline (≥30 msec and ≥60 msec) will be summarized as well.

7.12.5 Other Observations Related to Safety

Shifts from baseline to the worst post-baseline ECOG score will be tabulated.

7.13 [redacted]

Table 7.2 [redacted]

[redacted]

[redacted]

[redacted]

7.14 Changes in the Statistical Analysis Plan

See Section 1.2 for summary of changes.

8.0 REFERENCES

1. Babb J, Rogatko A, Zacks S (1998), "Cancer phase I clinical trials: efficient dose escalation with overdose control", Statistics in Medicine,17(10):1103-20.
2. Brookmeyer R, Crowley J (1982), "A confidence interval for median survival time", Biometrics, Vol 38(1):29-41
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al (2009), "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)", Eur J Cancer, 45(2):228-47.
4. Neuenschwander B, Branson M, Gsponer T (2008), "Critical aspects of the Bayesian approach to phase I cancer trials", Statistics in Medicine, 27(13):2420-39.

Appendix A By-Subject Listings

In addition to the analysis outputs outlined above in the main text, separate by-patient listings will also be generated to include the following information:

- Disposition (date of first dose, date of last dose, number of cycles, reason for discontinuation of study treatment).
- Analysis populations.
- Significant protocol deviations.
- Demographics and Baseline characteristics
- Disease characteristics
- Medical history and Concomitant medical conditions
- Medication history and Concomitant Medication
- Prior therapies
- Study drug exposure.
- TEAEs.
- TEAEs leading to study drug discontinuation.
- TEAEs resulting in dose modifications (delay, interruption, or reduction).
- Grade 3 or higher TEAEs.
- Vitals signs for those patients with clinically relevant changes in blood pressure during the infusion:
  - Increase of diastolic blood pressure of at least 10 mm Hg during any infusion.
  - Decrease of diastolic blood pressure of at least 10 mm Hg during any infusion.
  - Increase of systolic blood pressure of at least 20 mm Hg during any infusion.
  - Decrease of systolic blood pressure of at least 20 mm Hg during any infusion.
- Serious AEs.
- Lab measurements.
- Vital signs
- All deaths
- On-study death
- DLTs during Cycle 1 in dose escalation and expansion safety lead-in.
- Pharmacokinetic concentrations.

- Pharmacokinetic parameters.
- ADA.
- Efficacy (response assessments by mRECIST v1.1 and iRECIST criteria, best overall response, sum of target lesion diameter, status of non-target lesion, status of new lesion, all time to events).

Appendix B Date Imputation Rules

Incomplete Dates in the Screening Period

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used.

Incomplete Adverse Event Onset Date

Assumption: For on-study Adverse Events.

If *year* is missing (or completely missing): set to the date of first dose.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

If *month* and *year* are present and *day* is missing:

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

For all other cases: set to date of first dose.

Incomplete Adverse Event Resolution Date

Assumption: For on-study Adverse Events

If *day* is missing but *month* and *year* are non-missing, impute as the earliest of:

Last day of the *month*

Date cutoff date

Death date

If *day* is missing but *month* and *year* are non-missing, impute as the earliest of:

December 31st

Date cutoff date

Death date

Incomplete Concomitant Medication Start Date/Prior Therapy Start Date/Progression Date during Prior Anti-Cancer Therapy

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to January 1st.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month.

Incomplete Concomitant Medication End Date

If *year* is missing (or completely missing): do not impute.

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

Set *month* and day to December 31st.

If *year* and *month* are present and *day* is missing:

Set *day* to last day of the month.

Incomplete Subsequent Anti-Cancer Therapy Start Date

If *year* is missing (or completely missing): set to date of last dose of study treatment + 1

If (*year* is present and *month* and *day* are missing) or (*year* and *day* are present and *month* is missing):

If *year* > year of the last dose: Set *month* and *day* to January 1st.

If *year* = year of the last dose: Set *month* and *day* to date of last dose of study treatment +1.

If *year* and *month* are present and *day* is missing:

Set *day* to 1st day of month if the resulting imputed date is greater than date of last dose.

Otherwise set the imputed date to date of last dose + 1.

Appendix C Description and Operating Characteristics of the BLRM for Dose Escalation

An adaptive BLRM with overdose control principle is used to guide dose escalation decisions and MTD estimation, along with considerations of other emerging safety, clinical, PK, and pharmacodynamic data.

The 2-parameter logistic regression model used is as follows:

$$logit(\pi_i) = \log(\alpha) + \beta \log\left(\frac{dose_i}{dose_{ref}}\right), \alpha > 0, \beta > 0,$$

where π_i is the DLT rate for $dose_i$, and $dose_{ref}$ is the reference dose. A quantile-based, weakly informative, bivariate normal prior will be used for ln(α) and ln(β). This prior will be assigned based on pre-study estimates of median DLT at the provisional dose levels as shown in Table 1 (described by Neuenschwander et al. 2008).

Table 1 Prior Median and 95% Credible Interval for DLT Probabilities at Each Dose Level

Dose Level (mg/kg)	Median DLT Rate	95% Credible Interval for DLT Rate
0.1	0.05	(0, 0.90)
0.2	0.10	(0, 0.92)
0.4	0.20	(0, 0.94)
0.75	0.25	(0, 0.95)
1.5	0.30	(0, 0.96)
3	0.45	(0.01, 0.97)
6	0.50	(0.02, 0.98)

DLT: dose-limiting toxicity.

The model will be updated after each group of approximately 3 patients is enrolled in the current dose level. Each subject will participate in only 1 dose cohort. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0,0.16): under-toxicity.
- [0.16, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The simulations to evaluate the operating characteristics are based on provisional dose levels (0.1, 0.2, 0.4, 0.75, 1.5, 3, 6 mg/kg), representing the various distributions of toxicity across dose levels, detailed as shown in Table 2.

Table 2 Dose Escalation Simulation Study of the Probability of DLT

	True P(DLT) at each scenario					
Dose Level (mg/kg)	1	2	3	4	5	6
0.1	0.001	0.01	0.05	0.10	0.25	0.50
0.2	0.02	0.05	0.10	0.20	0.45	0.60
0.4	0.04	0.10	0.20	0.30	0.52	0.70
0.75	0.06	0.20	0.25	0.45	0.60	0.75
1.5	0.08	0.23	0.30	0.55	0.70	0.85
3	0.10	0.26	0.45	0.65	0.80	0.90
6	0.12	0.30	0.50	0.75	0.90	0.99

DLT: dose-limiting toxicity.

The trend of the dose-DLT relationship becomes steeper and MTD is reached earlier from Scenario 1 to Scenario 6. Table 3 shows the operating characteristic results.

Table 3 Operating Characteristics for BLRM Dose Escalation Rule

	Probability of Recommending a:			Average Proportion of Patients Receiving a:			Average Number of Patients	
Scenario	**Low Dose**	**Target Dose**	**High Dose**	**Low Dose**	**Target Dose**	**High Dose**	**Per study**	**Experiencing DLT per study**
1	100.0	NA	NA	100.0	NA	NA	24.2	1.5
2	16.2	83.8	NA	47.2	52.8	NA	21.4	3.4
3 [a]	16.1	75.7	6.5	38.7	53.5	7.8	18.9	3.8
4 [b]	12.8	70.3	11.4	28.5	53.8	17.6	16.1	3.9
5 [c]	NA	42.0	16.1	NA	61.7	38.3	10.6	3.7
6 [d]	NA	NA	10.2	NA	NA	100.0	5.9	3.0

BLRM: Bayesian Logistic Regression Model; DLT: dose-limiting toxicity.
Low dose = true DLT rate is [0, 0.16]; target dose = true DLT rate is [0.16, 0.33]; high dose = true DLT rate is [0.33, 1.00].
a Probability of 1.7% to claim all doses are toxic.
b Probability of 5.5% to claim all doses are toxic.
c Probability of 41.9% to claim all doses are toxic.
d Probability of 89.8% to claim all doses are toxic.

In Scenario 1 where all true DLT rates are below 0.33, the average number of patients required is approximately 24 with 1.5 DLTs expected on average.

The true DLT rates in Scenario 2 increase faster than Scenario 1 but are still all below 0.33, and the BLRM has an 83.8% chance of successfully recommending target dose levels. The average number of patients required is approximately 21, with 3.4 DLTs expected on average.

In Scenario 3, there is a 16.1% chance of recommending a lower dose as MTD and a 75.7% chance of successfully recommending target dose levels. The average number of patients required is approximately 19, with 3.8 DLTs expected on average.

In Scenario 4, with a faster increase of DLT rate over doses, there is 70.3% chance of claiming the target doses as MTD, an 11.4% chance of recommending a toxic dose, and approximately a 5.5% chance of claiming all doses are toxic. The average number of patients required is approximately 16 with 3.9 DLTs expected on average.

Scenario 5 further increases the DLT rate over dose levels and has a 42.0% chance of recommending a target dose level as MTD, a 16.1% chance of recommending a toxic dose, and a 41.9% chance of claiming all doses as toxic. This scenario requires, on average, approximately 11 patients, and results in 3.7 DLTs on average.

When all doses are toxic, as in Scenario 6, there is an 89.8% chance of successfully claiming all doses are toxic. The average number of patients required is approximately 6 and 3.0 DLTs are expected on average.

The accuracy of the BLRM recommendation relies on the true DLT rate; thus, the safety, clinical, PK, and pharmacodynamic data evaluation are combined to support the dose escalation. As an example, a hypothetical dose escalation is shown in Table 4 to illustrate how BLRM guides dose escalation.

Table 4 Hypothetical Dose Escalation Steps

Step	Dose (mg/kg)	#patients	#DLTs	Next Recommended Dose (mg/kg)
1	0.1	3	0	0.2
2	0.1	3	0	
	0.2	3	1	0.4
3	0.1	3	0	
	0.2	3	1	
	0.4	3	0	1.5
4	0.1	3	0	
	0.2	3	1	
	0.4	3	0	
	0.75	3	2	0.4
5	0.1	3	0	
	0.2	3	1	
	0.4	6	2	
	0.75	3	2	0.2
6	0.1	3	0	
	0.2	6	1	
	0.4	6	2	
	0.75	3	2	0.2 mg/kg is claimed as the MTD

DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

In addition, the BLRM is flexible in handling late-onset toxicities and can be fed with events meeting DLT criteria but occurring in later cycles to modulate dose escalation, as needed.