Clinical Study Protocol

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

Document Version and Date: Amendment 6.0, 28 July 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

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

A Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study

Sponsor:	Takeda Development Center Americas, Inc. (TDCA) Lexington, MA
Study Number:	TAK-573-1001
Compound:	Modakafusp alfa (TAK-573)
Date:	28 July 2022 **Amendment Number:** 06

Amendment History:

Date	Amendment Number	Region
28 July 2022	6	Global
16 November 2021	5	Global
11 August 2021	4	Global
08 March 2021	3	Global
12 March 2020	2	Global
22 October 2019	1	Global
05 August 2019	Initial Protocol	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the Study Manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

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

[redacted], MD Date
Program Clinical Lead

[redacted], MD, PhD Date
Clinical Study Lead

[redacted], PhD Date
Quantitative Clinical Pharmacology

[redacted], PhD Date
Statistical and Quantitative Sciences

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs are defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix C).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 6 Summary of Changes

This section describes the changes in the protocol incorporating Amendment 6. The primary reasons for this amendment are to:

- Update "modified Response Evaluation Criteria in Solid Tumors" (mRECIST) criteria to "Response Evaluation Criteria in Solid Tumors" (RECIST) throughout the protocol.
- Define the number and timing of prior lines of anti-PD1 therapy permitted for enrollment into the phase 2 dose expansion cohorts.
- Exclude enrollment of patients with acral lentiginous melanoma into some parts of the study.
- Exclude enrollment of patients with a history of immune-related adverse events (AEs) related to anti-PD1/PD-L1 treatment that required treatment discontinuation.
- Clarify the timing of pregnancy tests and that pregnancy tests can be urine or serum.
- Clarify the exclusion criteria regarding a prohibited history of immune-related AEs and exclusion for persistent toxicity.
- Update excluded concomitant medications regarding exceptions for chronic concomitant steroid usage.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 6			
Summary of Changes Since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	2.0 Study Summary 7.1 Inclusion Criteria 7.2 Exclusion Criteria	Restrictions for pregnancy, sperm/ova donation, and breastfeeding during and after study participation were revised.	Update.
2.	2.0 Study Summary 7.1 Inclusion Criteria	The number and timing of prior lines of anti-PD1 therapy permitted for enrollment into the phase 2 dose expansion cohorts I and II were clarified or revised.	Update.
3.	2.0 Study Summary 7.2 Exclusion Criteria	Patients with acral lentiginous melanoma are excluded in phase 2 except for the safety lead-in phase.	Update.

Protocol Amendment 6			
Summary of Changes Since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	2.0 Study Summary 7.2 Exclusion Criteria	Exclusion criterion #5 regarding a history of immune-related AEs related to treatment with prior checkpoint inhibitor was changed to exclude a history of immune-related AEs related to anti-PD1/PD-L1 treatment that required treatment discontinuation (phase 2).	Clarification.
5.	7.2 Exclusion Criteria	Exclusion #2 for persistent toxicity updated.	Update.
6.	2.0 Study Summary 7.2 Exclusion Criteria	Pregnancy tests can be urine or serum.	Clarification.
7.	2.0 Study Summary 7.2 Exclusion Criteria 8.9.1 Contraception and Pregnancy Avoidance Procedures9.3.9 Pregnancy Testing 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Gender-neutral language was applied.	Update.
8.	10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	The time period for reporting pregnancies on study was updated.	Update.
9.	8.9.1 Contraception and Pregnancy Avoidance Procedures	New section and table added to clarify highly effective contraceptive measures.	Update.
10.	8.7 Excluded Concomitant Medications and Procedures	Exceptions for chronic concomitant steroid usage updated.	Update.
11.	8.8.1 Premedication	Revised the requirements for premedications.	Update.
12.	8.10.1 Infusion-Related Reactions	Revised recommendations for managing IRRs.	Update.

Protocol Amendment 6			
Summary of Changes Since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	2.0 Study Summary 9.3.14 Disease Assessment Table 16.a Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 (Phase 1b Dose Escalation) Table 16.b Schedule of Events, Continued: Cycle 3 Through Cycle 6 (Phase 1b Dose Escalation) Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation) Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion) Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Reference for immune RECIST criteria added, and mRECIST updated to RECIST.	Update.
14.	9.3.14 Disease Assessment Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion) Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Guidelines for the use of contrast-enhanced computed tomography scans were revised.	Update.
15.	Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion) Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Timing of required pregnancy tests was clarified.	Clarification.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

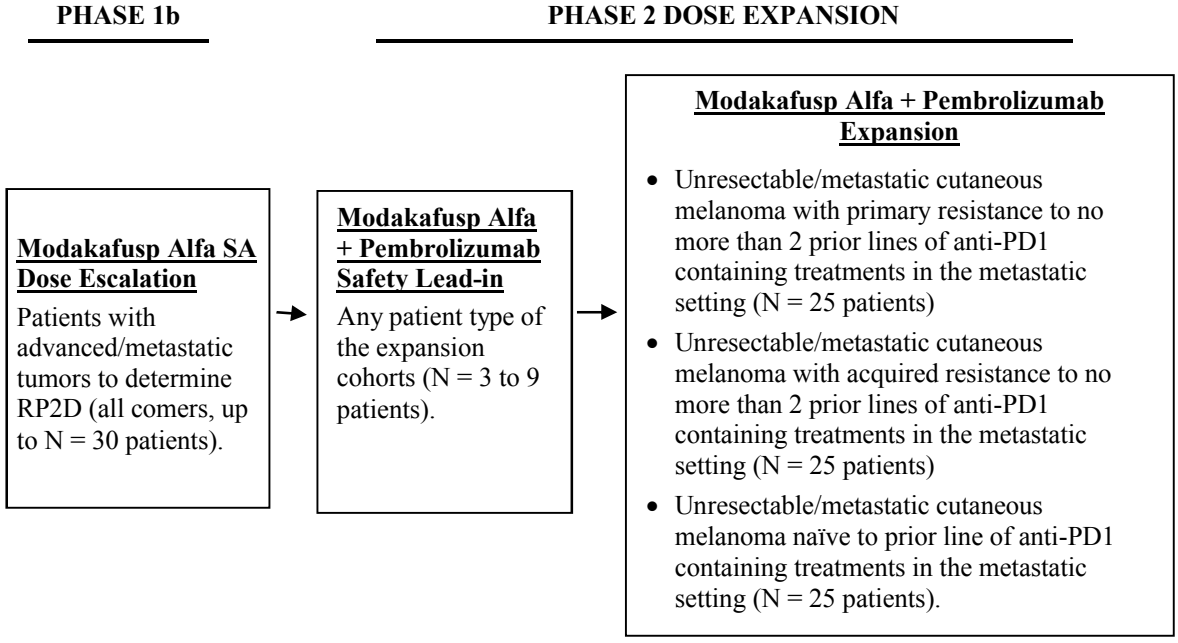
2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDCA)	**Compound:** Modakafusp alfa (TAK-573), henceforth referred to as "modakafusp alfa."
Title of Protocol: 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	**EudraCT No.**: Not applicable
Study Number: TAK-573-1001	**Phase:** 1b/2

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.



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 SA 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 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 at the SA starting dose of modakafusp alfa 0.1 mg/kg administered once 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. 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 dose-related toxicity, exposure, or pharmacodynamics. It is estimated that approximately 30 patients will be enrolled until either the MTD and/or PAD is identified.

Phase 2 Dose Expansion

Enrollment into Phase 2 expansion in combination with pembrolizumab 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 safety-lead in period to evaluate safety and tolerability during the Cycle 1 dose-limiting toxicity (DLT) evaluation period of modakafusp alfa 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 once every 6 weeks (Q6W), the combination dose and regimen could be selected for the 3 expansion 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 one dose lower than that of the modakafusp alfa RP2D in combination with pembrolizumab. Other approved dosing regimens (eg, 200 mg Q3W) for pembrolizumab 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 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, 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 line of anti-PD1 containing treatments in the metastatic setting.

A Bayesian predictive probability design will be used to allow multiple futility analyses for early termination due to futility. Up to 25 patients will be enrolled in each cohort in phase 2.

Primary Objective:

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 only).

Secondary Objectives:

- To define the MTD and/or 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) or 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).

Patient Population

For both phase1b and phase 2 of the study, eligible patients must have histologically confirmed advanced (locoregionally recurrent, not amenable to curative therapy) or metastatic solid tumors. Please see below for eligibility criteria.

Phase 1b Dose Escalation: Patients with locally advanced or metastatic solid tumors.

Phase 2 Dose Expansion:

The combination cohorts, including patients in the safety-lead phase, will enroll patients with one of the following 3 disease indications:

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.

Please refer to the Eligibility Section for Inclusion and Exclusion details.

Number of Patients:	**Number of Sites:**
Phase 1b Dose Escalation: ~30 patients Phase 2 Dose Expansion: 3 to 9 safety lead-in patients for combination therapy; 25 patients for each expansion cohort (3 cohorts) = ~84 patients. Total: up to ~ 114 patients.	Phase 1b Dose Escalation: approximately 3 to 4 sites. Total number of sites: up to approximately 22.
Dose Level(s): Modakafusp alfa: 0.1, 0.2, 0.4, 0.75, 1.5, 3.0, and 6.0 mg/kg in a 21-day treatment cycle. Pembrolizumab: 400 mg in a 6-week treatment cycle.	**Route of Administration:** Modakafusp alfa: Intravenous (IV) Pembrolizumab: Intravenous (IV)
Duration of Treatment: Patients may receive SA modakafusp alfa for 1 year or modakafusp alfa in combination with pembrolizumab for up to 2 years. Patients with demonstrated clinical benefit can continue treatment beyond this point if approved by the sponsor.	**Period of Evaluation:** The estimated time frame for study completion is 55 months (12 months of enrollment in escalation, 18 months of enrollment in expansion, 24 months of treatment, and 1 month of follow-up).

Main Criteria for Inclusion:

1. Adult patients aged ≥18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
3. Life expectancy >12 weeks according to investigator's judgment.
4. Phase 1b dose escalation: Eligible patients must have histologically confirmed advanced (locoregionally recurrent, not amenable to curative therapy) or metastatic solid tumors.
5. Measurable disease per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). At least 1 target lesion amenable for biopsy is required for enrollment in phase1b. A minimum of 1 target lesion for response assessment is required for enrollment in phase 2. A separate lesion amenable for biopsy is required for enrollment in phase 2 for cohort I and II (post futility analysis) and all patients (safety-lead in and expansion) with subgroup cohort III melanoma.
6. Phase 1b Dose Escalation: Patients with histologically confirmed advanced locally (locoregionally recurrent, not

amenable to curative therapy) or metastatic solid tumors.

Phase 2 Dose Expansion:

The combination cohorts, including patients in the safety-lead phase, will enroll patients with unresectable/metastatic melanoma in the following 3 subgroups:

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

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

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

- Patients with BRAF V600E mutant melanoma may have received prior BRAF inhibitor therapy.
- For cohorts I and II, there is no limitation of total number of prior line(s) of therapy, but the number of prior line(s) containing anti-PD1 must be ≤2 in the metastatic setting.
- For cohort III, patients who received an anti-PD-1 treatment in the adjuvant setting must have completed that treatment at least 6 months prior to enrollment and must not have progressed on the anti-PD1 adjuvant treatment.
- Primary resistance is defined as a best response of PD or SD<6 months to an anti-PD1 alone or in combination with other agents (ie, CTLA4) in the initial anti-PD1 containing treatment.
- Acquired resistance is defined as progression following a best response of CR, PR, or SD >6 months to a prior anti-PD1 alone or in combination with other agents (ie, CTLA4).

7. Reproductively female patients who:
   - Are postmenopausal for at least 2 years before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, due to unknown risks and potential harm to an unborn child/infant, must agree to the following:
     – Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 7 days after the last dose of modakafusp alfa or 4 months after the last dose of pembrolizumab, whichever is longer, OR
     – Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
     – Agree not to donate an egg or eggs (ova) or breastfeed a baby during the study through 7 days after the last dose of modakafusp alfa and 4 months after the last dose of pembrolizumab, whichever is longer.
8. Reproductively male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the study and through 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab) OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
   - Agree not to donate sperm during the study and through 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab).
9. Voluntary written consent must be given before performance of any study-related procedure not part of standard

medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

10. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
    - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, platelet count $\geq 75.0 \times 10^9$/L, and hemoglobin ≥80 g/L without growth factor or transfusion support for ANC and platelets in the preceding 2 weeks.
    - Total bilirubin ≤1.5 times the upper limit of normal (ULN).
    - Serum alanine aminotransferase or aspartate aminotransferase ≤3.0 times the ULN (<5 times the ULN if liver enzyme elevations are due to liver metastases).
    - Creatinine <1.5 times the ULN or estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (Levey et al. 2006) or Chronic Kidney Disease Epidemiology Collaboration (Levey et al. 2009) equations.
11. Patients must agree to the applicable biopsy requirements as detailed in the Schedule of Events.

Main Criteria for Exclusion:

1. Treatment with any SoC or investigational anticancer drug within 28 days or 5 half-lives before administration of modakafusp alfa, whichever came first. The washout period is 3 weeks for previous major surgery, 2 weeks for previous radical radiation (including chemoradiation and whole-brain radiation), and 5 days from last dose for focal radiation for symptomatic metastases.
2. Persistent toxicity from previous treatments that has not resolved to ≤ National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 (NCI CTCAE v.5) Grade 1 prior to administration of modakafusp alfa, except for alopecia, G2 neuropathy, and G2 asthenia/fatigue.
3. History of any of the following ≤6 months before first dose: New York Heart Association Grade III or IV congestive heart failure, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, any ongoing symptomatic cardiac arrhythmias of Grade >2, pulmonary embolism, or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, symptomatic pericardial effusion or restrictive cardiomyopathy). Chronic, stable atrial fibrillation on stable anticoagulant therapy, including low molecular-weight heparin, is allowed.
4. Baseline QT interval corrected by the Fridericia method (QTcF) >480 msec (Grade ≥2), history of congenital long QT syndrome, or torsades de pointes.
5. History of immune-related AEs related to anti-PD1/PD-L1 treatment that required treatment discontinuation (phase 2).
6. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of adverse events (AEs) or has compromised ability to provide written informed consent.
7. History of uncontrolled brain metastasis or previously treated metastases receiving corticosteroid dose ≥20 mg/day of prednisone equivalent at the time of receiving the first dose of modakafusp alfa. *Note:* Patients with carcinomatosis meningitis or leptomeningeal disease are excluded, regardless of clinical stability.
8. Patients with uveal (ocular) or mucosal melanoma are excluded (phase 2).
9. Patients with acral lentiginous melanoma are excluded in phase 2 except for the safety lead-in phase.
10. Ongoing or active infection.
11. Known history of HIV infection or any other relevant congenital or acquired immunodeficiency.
12. Known hepatitis B (HBV) surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have a positive HBV core antibody can be enrolled but must have an undetectable hepatitis B viral load.
13. Autoimmune disease requiring systemic immunosuppressive therapy. Patients with immune mediated endocrine deficiency from previous therapy with stable hormone replacement are exceptions.
14. History of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in modakafusp alfa or pembrolizumab formulation.
15. Patients who are lactating and breastfeeding or have a positive serum or urine pregnancy test during the screening period.

Main Criteria for Evaluation and Analyses:

The primary endpoints are:

- Frequency and severity of TEAEs according to NCI CTCAE v.5 (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 RECIST V1.1 for melanoma patients (phase 2 expansion).

The secondary endpoints are:

- MTD or PAD, if available (phase 1b).
- RP2D (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 for dose escalation phase (phase 1b) and safety lead-in phase of dose expansion (phase 2 safety-lead in):
  - 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 RECIST v1.1 for dose escalation phase (phase 1b).
- Disease control rate (DCR) (CR + PR + stable disease [SD]) (phase 1b and phase 2 expansion).
- DOR (phase 1b and phase 2 expansion).
- Time to progression (TTP) (phase 1b and phase 2).
- Progression-free survival (PFS) assessed according to RECIST v1.1. (phase 1b and phase 2 expansion).
- 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 expansion).

Statistical Considerations:

An adaptive BLRM that implements EWOC will be used for dose escalation recommendations and estimation of the MTD starting with the second dose level. In dose escalation, the PK parameters will be summarized using descriptive statistics. Individual modakafusp alfa concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

Primary efficacy endpoints include ORR for melanoma patients in the expansion cohorts. Secondary efficacy endpoints include ORR for patients in phase 1b dose escalation, DCR, DOR, TTP, PFS, and OS. No formal statistical tests will be performed for these efficacy endpoints. ORR and DCR will be summarized using descriptive statistics

with 95% CIs. PFS and OS will be analyzed descriptively using the Kaplan-Meier method for the safety analysis set. DOR will also be analyzed using the Kaplan-Meier method for the response-evaluable analysis set.

Sample Size Justification:

It is expected that approximately 30 patients will be enrolled in the phase 1b escalation phase. A minimum of 3 patients will be enrolled at the starting dose level. Starting from the second dose level, an adaptive BLRM guided by the EWOC principle will be used for all subsequent dose escalation recommendations.

Up to 25 patients will be enrolled in each of the 3 combination therapy cohorts. A Bayesian predictive probability design was used to allow multiple interim analyses for early termination due to futility. Assuming 3 to 9 safety lead-in patients, the total sample size for phase 2 can be up to 84.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in Appendix C (Responsibilities of the Investigator). The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

	Term
ADA	antidrug antibody
ADR	adverse drug reaction
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
AUC_{last}	area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_t	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
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed serum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
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
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
IB	Investigator's Brochure

	Term
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IFNα	interferon-alpha
IFNα2b	interferon-alpha 2b
Ig	immunoglobulin
IL	interleukin
IND	investigational new drug
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IV	intravenous(ly)
IVIG	intravenous immunoglobulins
KD	disassociation constant
mAb	monoclonal antibody
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NLCB	no longer clinically benefitting
NSCLC	non–small-cell lung cancer
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cell
PD	progressive disease; disease progression
PFS	progression-free survival
[redacted]	[redacted]
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
QTcF	QT interval with Fridericia correction method
Q3W	once every 3 weeks
Q6W	once every 6 weeks

	Term
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
SSE	symptomatic skeletal event
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TAK-573	modakafusp alfa
TBNK	quantification of T cells, B cells, and natural killer cells
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed serum modakafusp alfa concentration
TME	tumor microenvironment
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state

3.4 Corporate Identification

TDC Takeda Development Center Americas, Inc. (TDCA)

4.0 INTRODUCTION

4.1 Modakafusp Alfa (TAK-573) Background

Modakafusp alfa (TAK-573), henceforth referred to as "modakafusp alfa," is a recombinant humanized immunoglobulin (Ig) G4 anti-CD38 monoclonal antibody fused to 2 attenuated interferon-alpha 2b (IFNα2b) moieties. Modakafusp alfa is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. The CD38 antibody portion of modakafusp alfa directs the attenuated IFNα2b portion to CD38-expressing (CD38+) cells, thus achieving a high local concentration of IFNα2b at the surface of these target cells. On CD38-negative cells, the attenuation results in approximately 130,000-fold reduced potency compared with IFNα2b.

Modakafusp alfa has a high binding affinity (dissociation constant [KD]) for human and cynomolgus CD38, with a KD of 168 pM and 1.25 nM, respectively. Modakafusp alfa can potently inhibit proliferation of CD38+ multiple myeloma (MM) cells (half-maximal inhibitory concentration [IC_{50}] 19.9 pM), whereas potency on CD38-negative cells is approximately 2500-fold lower. The antibody portion of modakafusp alfa is an IgG4 isotype (unlike the IgG1 isotype of daratumumab) and therefore has limited effector capacity to induce antibody-dependent cell mediated cytotoxicity, antibody-dependent cellular phagocytosis, or complement activation against normal CD38+ cells. Modakafusp alfa does not modulate the adenosine diphosphate-ribosyl cyclase activity of CD38, unlike daratumumab.

Interferon-α2b (Intron A) by comparison has similar potency to modakafusp alfa on CD38+ cells (IC_{50} 12.3 pM) but on CD38-negative cells is approximately 130,000-fold more potent than modakafusp alfa (EC_{50} [half-maximal effective concentration] ~0.37 pM).

A brief background of modakafusp alfa is provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

4.1.1 Modakafusp Alfa Targets

The tumor cell surface-expressed antigen CD38 is uniformly and highly expressed on multiple myeloma (MM) cells (Lin et al. 2004; Santonocito et al. 2004) and at lower levels on various lymphoid and myeloid cells and some solid organs (Deaglio et al. 2008). Being highly expressed on the myeloma cell surface and showing lower expression on normal cells makes CD38 an appropriate target for delivering drugs (cytokines, radioisotopes (Green et al. 2014), and toxins (Bolognesi et al. 2005; Goldmacher et al. 1994) to receptor-expressing cells. A promising moiety to be conjugated to an anti-CD38 monoclonal antibody (mAb) is the cytokine interferon-alpha (IFNα), which is currently approved—although seldom used—for maintenance treatment for MM, metastatic melanoma, follicular lymphoma, or hairy cell leukemia. IFNα has direct inhibitory effects on some tumors and is a potent stimulator of both the innate and adaptive immune systems. Systemic toxicity of IFN-α, however, precludes the use of the cytokine at therapeutically effective doses in the majority of patients. By reducing the binding affinity of IFNα (KD) for its IFNα receptor, modakafusp alfa is expected to limit binding of attenuated IFNα to its receptor on

non-CD38-\-expressing cells. In contrast, binding of modakafusp alfa with high affinity via its CD38 targeting moieties is expected to increase the local concentration of attenuated IFNα on CD38+ target cells, thereby inducing desired on-target interferon (IFN) pathway activation. In addition, IFNα pathway activation induces up-regulation of CD38 messenger RNA and protein levels in malignant cells of patients with B cell chronic lymphocytic leukemia (Bauvois et al. 1999), suggesting that modakafusp alfa may be able to increase CD38 target expression in MM and other CD38+ immune cells, thus overcoming the limitations seen with drugs such as daratumumab which depletes CD38+ immune cells. modakafusp alfa increases CD38 expression on MM cells in vitro, which further supports this hypothesis.

CD38 is a multifunctional ectoenzyme involved in cell adhesion and transmembrane signaling. It is overexpressed in hematologic tumors, where it is believed to play a role in tumor cell migration and metastasis. CD38 has been reported to be highly expressed in the majority of MM patient-derived tumor cells (Lin et al. 2004). CD38 is an approximately 45 kDa transmembrane glycoprotein expressed by immature hematopoietic cells, downregulated in mature cells, and re-expressed at higher levels by activated lymphocytes, such as T cells, B cells, dendritic cells, and natural killer (NK) cells (Funaro et al. 1990).

Early bone marrow cells, which are crucial for long-term (sustained) marrow recovery, do not express CD38, but committed progenitor bone marrow cells, B cells in germinal centers, terminally differentiated plasma cells, and activated tonsils are CD38+ (Chillemi et al. 2013). Deaglio et al (Deaglio et al. 2008) reviewed the main tissues and cells where CD38 is present, as summarized in Table 4.a. CD38 is also found in a soluble form in normal and pathological fluids (2018).

Recent data suggests that CD38 is a major mechanism of acquired resistance to PD1/PD-L1 blockade, causing CD8+ T-cell suppression (Bauvois et al. 1999).

Table 4.a Reported Distribution of Human CD38

Tissue	Cellular Distribution	Putative Function
Bone marrow	Hematologic precursors plasma cells	Homing and apoptosis; marker of precursor cell commitment
Thymus	Throughout thymic development	Unknown
Spleen/lymph nodes	Germinal center B cells	Rescue from apoptosis
Blood	T, B, NK, and monocyte subsets; platelets and erythrocytes; hematologic precursors plasma cells	Interaction with endothelium
Gut	Intraepithelial and lamina propria lymphocytes	Mucosal immunity
Brain	Purkinje cells; neurofibrillary tangles	Memory process
Prostate	Epithelial cells	Unknown
Pancreas	β cells	Insulin secretion
Bone	Osteoclasts	Bone resorptions
Eye	Retinal cells	Vision process
Muscle	Sarcolemma of smooth and striated muscle	Muscle contraction

Source: Deaglio et al 2008 (Deaglio et al. 2008).

4.1.2 Modakafusp Alfa Nonclinical Pharmacology

Modakafusp alfa effectively induces apoptosis in high-expressing CD38+ human myeloma cells as demonstrated in a caspase activation assay (EC_{50} 23 pM); no apoptotic effects are observed with normal human peripheral blood mononuclear cells (PBMCs). Modakafusp alfa elicited a low level of cytokine release (tumor necrosis factor alpha, interleukin [IL]-6, IL-8, interferon-gamma [IFN-γ], and IL-2) from human PBMCs in vitro and therefore, is unlikely to induce cytokine release syndrome (CRS) in the clinic.

Modakafusp alfa is active in multiple human myeloma xenograft models and induces complete regressions at tolerated doses. A single dose of 10 mg/kg modakafusp alfa in the NCI-H929 human myeloma xenograft model resulted in complete regressions in all treated animals. In comparative xenograft studies using the H929 model, modakafusp alfa had more robust antitumor activity than established myeloma therapies, including bortezomib, lenalidomide, and daratumumab. Furthermore, under conditions of suboptimal dosing of modakafusp alfa, strong synergy has been observed with other standard treatment agents such as bortezomib and lenalidomide. Details of these in vivo experiments can be found in the modakafusp alfa IB.

The nonclinical rationale for a potential antitumor benefit in patients with solid tumors is presented in detail in Section 4.4.1.

4.1.2.1 Toxicology Studies

A series of toxicological studies in cynomolgus monkeys was conducted [redacted].

No remarkable toxicity was noted following a single administration of modakafusp alfa at dose levels up to 20 mg/kg via 1-hour intravenous (IV) infusion. Neopterin levels (a biomarker of IFN biological activity) were measured; increases in neopterin were noted at 24 hours postdose and were still above baseline up to 240 hours postdose.

Three repeat-dose toxicity studies were performed in cynomolgus monkeys where modakafusp alfa was administered by a 1-hour IV infusion: a 15- or 22-day non-Good Laboratory Practice (non-GLP), dose range–finding, once-weekly or twice-weekly study at dose levels of 3 or 10 mg/kg; a pivotal, 29-day, GLP study at dose levels of 3, 10, or 30 mg/kg weekly; and a follow-up 4-week GLP study at dose levels of 0.3, 3, or 10 mg/kg weekly. The results of these 3 studies were similar; the results of the 29-day GLP study are discussed below.

Administration of modakafusp alfa in all groups was well tolerated in the pivotal GLP study after the first and second dose. During the third and fourth doses, clinical signs were noted at all dose levels during the infusion. Clinical signs ranged from mild to severe and consisted of 1 or more of the following: vomiting; retching; salivation; swelling of both eyelids; pallor of the lips, muzzle, and chin; increased activity; presence of red spots on the limbs and axillary, inguinal, and urogenital areas; vocalizing; piloerection; ptosis; coldness to touch; changes in activity; respiratory distress; and/or unresponsiveness. The majority of these clinical signs started at approximately 5 minutes after the start of infusion and mostly subsided on the same day; the exception was the presence of red spots, which persisted for 1 or 2 more days. During the third dose, the reaction was severe enough in 1 male at 30 mg/kg to require the cessation of dosing, after which the animal recovered. Diphenhydramine was administered 30 minutes before the start of the fourth dose on Day 22 (males only); however, immediately following the fourth dose, 4 males at the mid- and high-dose groups had severe reactions, and 3 were preterminally euthanized. The study was terminated before the fourth dose in females.

The weight of evidence is consistent with these responses being the result of secondary effects arising from antidrug antibody (ADA) formation and not a direct effect of modakafusp alfa. Concurrent with the onset of clinical signs during or shortly after the third and/or fourth dose, all animals had developed ADAs that were associated with decreased or undetectable exposure to modakafusp alfa and decreasing levels of the IFN biomarker neopterin, which were markedly elevated after the first and second doses. This antibody response included IgE class antibodies and activation of complement (increases in Bb and SC5b-9 split products of the complement pathway). Macroscopic and microscopic pathology findings unique to preterminally euthanized animals consisted of lung edema and vascular leukocytosis in the lung and liver, which likely contributed to the poor clinical condition and death of the animals, as well as minimal hematopoietic hypocellularity in the bone marrow.

Routine clinical chemistry examination of all animals done at weekly intervals was unremarkable except for an increase in total protein due to an increase in serum globulin content, a decrease in serum albumin (30 mg/kg females only), and a decreased albumin-globulin ratio at 10 and 30 mg/kg in females and at 30 mg/kg in males. These findings were consistent with an acute phase response and were accompanied by increases in C-reactive protein serum levels and elevations in

IL-6 in a total of 5 animals administered modakafusp alfa on Day 1 (1 animal) or Day 15 (4 animals). There were no modakafusp alfa–related increases in IFN-γ, TNF, IL-4, IL-5, or IL-2.

Additionally, minimal-to-slight decreases in total mean white blood cell counts and in neutrophils, lymphocytes, monocytes, eosinophils, basophils, and large unstained cells were noted on Days 2 and 7 in the animals administered modakafusp alfa in all dose groups. The decreases in leukocyte counts were not dose related and remained, for the most part, within the reference range.

From Day 14 to end of treatment ([EOT]; Day 23 for males and Day 24 for females), there were slight-to-moderate increases in mean leukocyte counts due to increases in lymphocytes, basophils, eosinophils, and large unstained cells in the animals administered modakafusp alfa in all dose groups, which were concurrent with the development of an ADA response. Additionally, there were decreases in red blood cell (RBC) counts, hemoglobin, and hematocrit with increased reticulocytes in all dose groups from Day 14 to EOT.

In all dose groups of both preterminally and terminally euthanized animals, macroscopic and microscopic changes were observed in the spleen and consisted of increased spleen weight correlating with follicular lymphoid hypercellularity, sinus histiocytosis, and sinus dilatation. The incidence and severity of lymphoid hypercellularity were generally proportional to dose, with no clear relationship to dose for sinus histiocytosis and dilatation. Concurrent follicular hyalinization or follicular lymphoid degeneration/necrosis was noted in 1 female dosed with 3 mg/kg and in 1 male dosed with 10 mg/kg, respectively. Bone marrow hematopoietic hypercellularity was present at 30 mg/kg. These histologic findings may have been partially confounded by the development of the ADA response. After a 21-day (males) or 28-day (females) recovery period, there was nearly complete recovery of splenic sinus dilation and complete recovery of all other spleen findings.

The marked immunogenic response of the monkeys to modakafusp alfa was not unexpected considering the presence of human IFN sequences, which are known to be highly immunogenic in monkeys, as is already known from previous experience with PEGIntron.

A no-observed-adverse-effect level was not identified in the pivotal GLP toxicity study, as adverse clinical signs were noted at the low dose of 3 mg/kg; however, 3 mg/kg was considered the highest nonseverely toxic dose.

4.2 Pembrolizumab Background

Pembrolizumab is a humanized immunoglobulin G4 (IgG4) mAb with a high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death protein 2 ligand (PD-L2). Preclinical data demonstrated the high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable clinical safety profile as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for treatment across multiple indications (Keytruda (pembrolizumab) PI 2018).

4.3 Known and Potential Benefits and Risks

4.3.1 Nonclinical Safety Summary of Modakafusp Alfa

Modakafusp alfa was initially considered a targeted therapy for CD38+ myeloma cells; however, effects on other CD38+ cells are possible and may give rise to toxicities related to the binding of modakafusp alfa and the effects of the attenuated IFN. The relevance of the majority of nonclinical toxicology findings in cynomolgus monkeys, attributed to effects related to ADA formation, is unclear because of a lack of predictivity of ADA activity in animals to humans. Additional information regarding benefits and risks to patients can be found in the modakafusp alfa IB.

4.3.2 Clinical Safety of Modakafusp Alfa

4.3.2.1 [redacted]

[redacted]

4.3.2.2 Study 1001

Seventeen patients were enrolled in Study 1001 as of the data cutoff of 23 January 2021 for preliminary analysis. The majority were white (88.2%) and male (58.8%). Patients ranged from 42 to 80 years of age, with a median of 64.0 years. Median duration of treatment overall was 3.14 weeks, and median number of treatment cycles received was 2. The majority of patients (70.6%) have discontinued study drug treatment, and 3 patients (17.6%) have discontinued the study. The primary reason for treatment discontinuation was progressive disease (75.0%).

All 17 patients (100%) in the study have experienced a TEAE. The most common TEAE was infusion-related reaction, which was reported in 8 patients (47.1%). Six patients (35.3%) had a TEAE of nausea, and TEAEs of chills, headache, and thrombocytopenia were each reported in 5 patients (29.4%).

Ten patients (58.8%) experienced an SAE, the most common of which was IRR (7 patients, 41.2%). All TEAEs of IRR were considered related to study drug. The only other SAE reported in more than 1 patient was muscular weakness, which occurred in 2 patients (11.8%).

4.3.3 Potential Effects Based on Nonclinical and Clinical Studies of Modakafusp Alfa

Lymphoid and Hematopoietic Effects

Slight decreases in white blood cells and RBCs mass were noted in the single-dose and repeat-dose nonclinical studies. These counts returned to baseline in the recovery phase.

[redacted]

As of the data cutoff of 23 January 2021, 5 patients (29.4%) in Study 1001 have experienced a TEAE of thrombocytopenia (including decreased platelet count), and in 1 patient (5.9%) the event was considered an SAE related to study drug. Neutropenia (including neutrophil count decreased) was reported in 3 patients (17.6%), all of which were ≥3 Grade and considered related to study drug. No patients discontinued study drug due to TEAEs of thrombocytopenia or neutropenia.

Elevations in Liver Enzymes

In nonclinical studies, minimal transient elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed in a few animals but lacked histopathologic correlates.

[redacted] One patient (5.9%) in Study 1001 had a TEAE of ALT increased, which was considered related to study drug and was not an SAE.

Infusion-Related Reactions

Infusion-related reactions (IRRs) ranging from mild to severe (including vomiting; retching; salivation; swelling of both eyelids; pallor of the lips, muzzle, and chin; increased activity; presence of red spots on the limbs and axillary, inguinal, and urogenital areas; vocalizing; piloerection; ptosis; coldness to touch; changes in activity; respiratory distress; and/or unresponsiveness) were observed in nonclinical studies in cynomolgus monkeys after repeat dosing and were attributed to secondary effects arising from ADA formation, rather than a direct effect of modakafusp alfa (Section 4.1.2.1). Reactions such as pyrexia, chills, nausea, vomiting,

flushing, dyspnea, cough, headache, dizziness, rash, and hypertension may occur following IV infusions across many drug classes.

[redacted]

As of the data cutoff of 23 January 2021, 8 out of 17 patients (47.1%) in Study 1001 experienced Grade 2 IRRs, and 7 of them were serious. All events were related to modakafusp alfa treatment. IRR-associated symptoms included uncoded (29.4%), chills (29.4%), nausea (17.6%), vomiting (11.8%), headache (11.8%), hypoxia (11.8%), back pain (11.8%), flushing (11.8%), abdominal pain (5.9%), tremor (5.9%), cough (5.9%), dyspnoea (5.9%), and sinus tachycardia (5.9%).

The sponsor strongly recommends the use of anti-inflammatory medications, including corticosteroids, prior to administration of modakafusp alfa in every cycle. Please see additional instructions about IRRs in Section 8.10.1. Permitted premedications are listed in Section 8.8.

Cytokine Release Syndrome

Modakafusp alfa elicited a low level of cytokine release (TNFα, IL-6, IL-8, IFN-γ, and IL-2) from human PBMCs in vitro, less than or comparable to that seen with Synagis (palivizumab, an IgG1 mAb against the syncytial respiratory virus), and is, therefore, unlikely to induce cytokine release syndrome (CRS) in the clinic. Minimal elevations in IL-6 were observed in nonclinical studies, with no modakafusp alfa-related effects on other cytokines tested (IFN-γ, TNF, IL-4, IL-5, or IL-2; IL-8 elevations were considered secondary to the antibody drug antibody response). CRS is being further evaluated in clinic. As of the data cutoff of 23 January 2021,1 patient in the Study 1001 experienced Grade 2 CRS, which was not serious.

Hypersensitivity Reactions

Severe immune-mediated (anaphylactic/anaphylactoid) reactions were observed in the pivotal 29-day GLP repeat-dose study in monkeys, attributable to the development of an ADA response including IgE class antibodies and/or activation of complement (Section 8.8.1). Although nonclinical ADA responses are not considered predictive of a human health risk, it is important to monitor for signs and symptoms of hypersensitivity reactions and treat accordingly.

Interference With Indirect Antiglobulin Tests (Indirect Coombs Test)

Interference with serological testing has been described with the anti-CD38 IgG1 antibody daratumumab, which binds to CD38 on RBCs and results in a positive indirect antiglobulin test (indirect Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

ADA Formation With Modakafusp Alfa

In the repeat-dose toxicology study in monkeys, all treated animals developed ADA. A decrease in modakafusp alfa serum concentrations and a decrease in neopterin (a biomarker of IFN biological activity) levels that correlated with measurable ADA titers were observed.

Based on available ADA data in Study 1001, six of eight (75%) patients were ADA positive post-treatment; all 6 patients were reported as ADA negative at baseline. No apparent dose-related increase in the ADA incidence was observed. The first incidence of ADA was observed at C2D1 for all post-treatment ADA, and both transient and persistent ADA were observed.

Exploratory analysis is going in the clinical studies to assess the impact of ADA on modakafusp alfa disposition, efficacy, and safety as more data are accrued.

4.3.4 Potential Effects of Pembrolizumab

Pembrolizumab toxicities are generally associated with the activation of autoreactive T-cells resulting in immune-related adverse events (irAEs) and embryofetal toxicity. The safety of pembrolizumab at 200 mg every 3 weeks or 400 mg every 6 weeks has been evaluated in multiple clinical studies, and the most common adverse drug reactions (ADRs) (≥20%) were fatigue, diarrhea, and nausea. The majority of ADRs reported were of Grade 1 or 2 in severity. For detailed information regarding the safety of pembrolizumab administration please refer to the Food and Drug Administration (FDA)-approved package insert (Keytruda (pembrolizumab) PI 2018).

4.3.5 Potential Overlapping Toxicities

Nonclinical toxicology studies evaluating the combination of modakafusp alfa and pembrolizumab were not conducted and are not warranted per ICH S9 (ICH 2018). Pembrolizumab is a mAb that binds to the human PD-1 receptor and blocks the interaction of PD-1 with PD-L1/PD-L2.

Modakafusp alfa and pembrolizumab both activate the immune system, so known PD-1 immunotherapy-related toxicities (eg, pneumonitis, colitis, hepatitis, dermatitis, IRRs, endocrinopathies, and nephritis) observed following the administration of pembrolizumab may be enhanced when combined with modakafusp alfa. Details regarding the full safety profile of pembrolizumab can be found in the FDA-approved package insert (Keytruda (pembrolizumab) PI 2018). To minimize the risk to patients treated with modakafusp alfa and pembrolizumab, phase 2 will include a safety lead-in phase for the combination cohorts to determine the safety and tolerability of the combination doses and regimen. Pembrolizumab will be administered at the approved dose and schedule of 400 mg IV once every 6 weeks (Q6W) to maximize the possibility of observing clinical benefit.

The safety of the pembrolizumab and pegylated interferon alfa-2b (PEG-IFN) combination was studied in 2 phase 1/2 studies. Seventeen patients were enrolled in the Keynote-029 trial (Atkins et al. 2018), 5 with melanoma and 9 with renal cell carcinoma (RCC). Across dose levels, the most common treatment-related AEs of any grade were fatigue (n = 11), 65%), pyrexia (n =7, 41%), chills, diarrhea and nausea (n = 6, 35% each). Grade 3 to 4 AEs were fatigue (n = 1), AST increase (n = 1), neutropenia (n = 1), and depression (n = 2). Forty-three patients with melanoma were enrolled in the Keynote-020 trial (Davar et al. 2018). The most frequent treatment-related toxicities were Grade 1 hyponatremia (11.1%), Grade 2 lymphopenia (10.8%), Grade 3 hyponatremia (10.3%), Grade 3 lymphopenia (12%) and Grade 3 fatigue (16.2%). Fifteen patients (34.9%) developed immune- related AEs (irAE) of any grade, including vitiligo (16.3%), hypothyroidism (16.3%), and one patient each with adrenal insufficiency (Grade 3), pneumonitis (Grade 4), and uveitis (Grade 4). No treatment-related deaths occurred.

4.3.6 Potential Pharmacokinetic Drug Interactions and Other Forms of Interaction

The potential for a direct PK drug-drug interaction between modakafusp alfa and pembrolizumab is likely low. Nevertheless, both pembrolizumab and modakafusp alfa are humanized IgG4 antibodies and, as such, potential ADA for modakafusp alfa generated against its IgG4 backbone may also impact the PK of pembrolizumab and vice versa. To assess the potential for immunogenicity drug-drug interaction between modakafusp alfa and pembrolizumab, serum PK of pembrolizumab when administered in combination with modakafusp alfa will be characterized in the study and compared with the reported pembrolizumab PK as monotherapy in solid tumor patients.

4.4 Rationale for the Proposed Study

4.4.1 General Rationale for Modakafusp Alfa in Solid Tumors

Pogue and colleagues previously indicated robust, complete antitumor responses in CD38-expressing, IFNα-sensitive xenograft models of MM following treatment with modakafusp alfa, driven by direct antiproliferative activity of IFNα and indirect activation of innate immune cell subtypes including M1 macrophage and NK cells (Pogue et al. 2016). [redacted]

Figure 4.a [redacted]

[redacted]

Figure 4.b [redacted]

[redacted]

4.4.2 [redacted]

[redacted]

[redacted]

4.4.3 Rationale for Phase 2 Expansion Phase Cohorts

Once a RP2D is defined in Phase 1b, enrollment will begin into phase 2 assessing the following cohorts 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.

In addition to the general rationale for modakafusp alfa in solid tumors presented in Section 4.4.1, rationales are presented in the indicated sections for patients with melanoma (Section 4.4.3.2) and for the combination with pembrolizumab [redacted]

Additional expansion arms exploring modakafusp alfa either as a single agent (SA) or as a combination may be added, based on information obtained during the dose-escalation or expansion phases.

4.4.3.1 [redacted]

[redacted]

[redacted]

4.4.3.2 Rationale for Treatment of Melanoma Patients with Modakafusp Alfa In Combination with a CPI

Immunotherapy with a checkpoint inhibitor (CPI) is safe and produces durable responses in 30% to 40% of patients with advanced melanoma (Larkin et al. 2015; Ribas et al. 2016). However, a significant portion of patients do not benefit from CPI treatment. For patients who progress after CPI, remaining options depend on the BRAF mutational status. A recent review of the published literature on CPI rechallenge indicated low response rates of 15% to 20% (Larkin et al. 2015; Ribas et al. 2016).

In addition to the general working hypothesis described in Sections 4.4.1 and 4.4.3.1, interest in the melanoma cohorts is supported by the work of Chen et al (Chen et al. 2018), which showed that CD38 expression is upregulated in preclinical NSCLC and melanoma tumor models after progression on CPI treatment and that this upregulation can be a mechanism of resistance to anti–PD-1/PD-L1 treatments. In vitro and in vivo studies demonstrate that CD38 inhibits CD8+ T-cell function via adenosine receptor signaling. The expression of CD38 in melanoma cancer cells may increase the targeting of modakafusp alfa to these resistant cells, providing additional opportunities for binding of attenuated IFN to IFNAR on these cancer cells. This mechanism of resistance to CPI has since been described in other tumor models.

Finally, exposure to modakafusp alfa increases PD-L1 expression in myeloma, and exposure to IFNα increases PD-L1 expression in human cancer, including melanoma.

Mechanism of resistance to CPI may be different in terms of acquired or primary resistance. Therefore 2 different expansion cohorts will assess modakafusp alfa and pembrolizumab in patients who initially responded or not to anti-PD-1 treatment (Blank et al. 2004; Iwai et al. 2002) (Vacchelli et al. 2015).

If the combination of modakafusp alfa and pembrolizumab is safe and a meaningful clinical activity is seen in melanoma, additional expansion cohorts assessing tumor types sharing the same rationale can be added.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to determine the safety and tolerability of modakafusp alfa as a 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).

5.1.2 Secondary Objectives

The secondary objectives are:

- To define the MTD and/or 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) or 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).

5.1.3 Exploratory/Additional Objectives

The exploratory/additional objectives are:

- To assess modakafusp alfa CD38 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 (as described above) 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).

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- Frequency and severity of TEAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5) (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 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) for melanoma patients (phase 2 expansion).

5.2.2 Secondary Endpoints

- MTD or PAD (as defined in 6.1.1), 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 v5 (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:
  - 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}).
- ORR (CR + PR) assessed according to the RECIST v1.1 for patients in dose escalation (phase 1b).
- Disease control rate (DCR) (CR + PR + stable disease [SD]) (phase 1b and phase 2).
- DOR (phase 1b and phase 2).
- TTP (phase 1b and phase 2).
- Progression-free survival (PFS) assessed according to RECIST v1.1 (phase 1b and phase 2)
- 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 Section 6.3.3.

5.2.3 Additional/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.

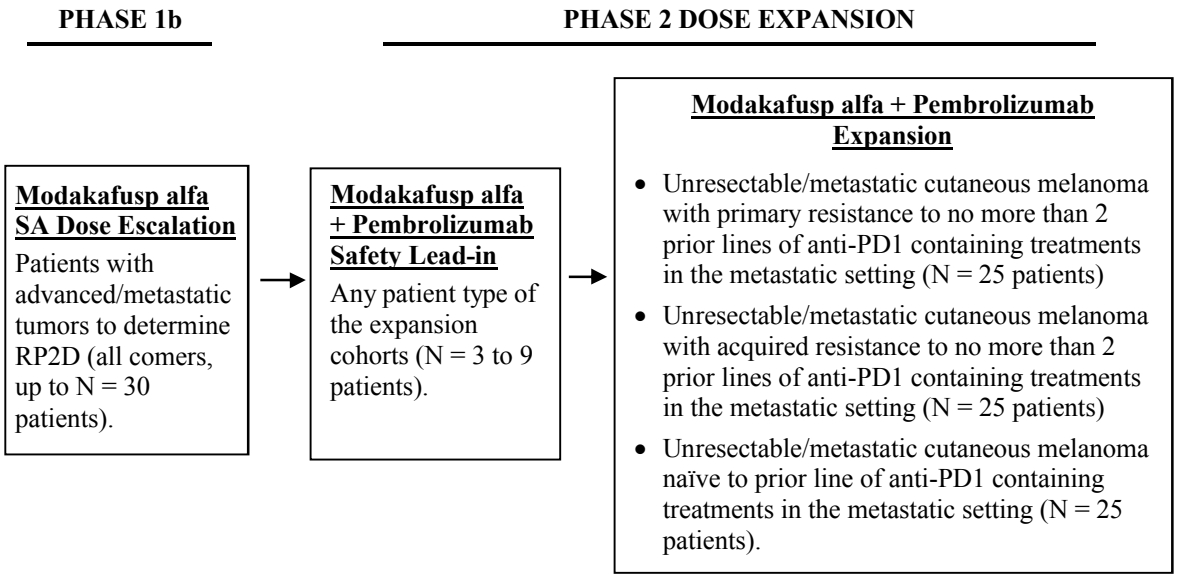
6.0 STUDY DESIGN

6.1 Overview of 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 SA and in combination with pembrolizumab in patients with advanced or metastatic solid tumors. Please see Section 7.0 for complete eligibility criteria.

The study consists of 2 phases as shown in Figure 6.a.

Figure 6.a Study Schema



RP2D: recommended phase 2 dose; SA: single agent.

6.1.1 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 SA RP2D and schedule of modakafusp alfa for further testing. The single-agent RP2D may be either the MTD based on DLTs or a 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 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. 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. It is estimated that approximately 30 patients will be enrolled until either the MTD and/or PAD is identified.

6.1.2 Phase 2 Dose Expansion

Enrollment into phase 2 expansion in combination with pembrolizumab will be initiated once the RP2D of modakafusp alfa 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 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 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 (eg, 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.

Up to 25 patients will be enrolled in each of the 3 cohorts in phase 2. A Bayesian predictive probability design will be used to allow multiple futility analyses for early termination due to futility.

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.

6.2 Number of Patients

It is expected that approximately 30 patients will be enrolled in the phase 1b dose escalation phase at approximately 3 to 4 sites. Up to 25 patients will be enrolled in each of the 3 combination therapy cohorts. A Bayesian predictive probability design was used to allow multiple interim analyses for early termination due to futility. Assuming 3 to 9 safety lead-in patients, the total sample size for phase 2 can be up to 84 patients.

The study is expected to enroll up to 114 patients overall.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive modakafusp alfa as a SA for up to 1 year or in combination with pembrolizumab for up to 2 years. Patients with demonstrated clinical benefit can continue treatment beyond those points if approved by the sponsor. These patients can continue receiving treatment in this study or in any of the poststudy access modalities described in the protocol (Section 6.3.5). Patients may discontinue treatment when they meet any of the discontinuation criteria stated in the protocol (Section 9.6).

All patients will have an EOT visit 30 days (+10 days) after receiving the last dose of study drug or before the start of subsequent systemic anticancer therapy, whichever occurs first, to permit detection of any delayed TEAEs and to resolve any ongoing events. Patients with unresolved TEAEs will continue the periodic safety follow-up until complete resolution or stabilization (established as sequelae) occurs.

Patients who discontinue study treatment for reasons other than progressive disease (PD) will continue PFS follow-up every 12 ± 1 weeks from the EOT visit until the occurrence of PD, lost to follow-up, consent withdrawal, death, start of subsequent systemic anticancer therapy, or study termination, whichever occurs first. After disease progression or starting another systemic anticancer therapy, all patients will be followed every 12 ± 1 weeks for OS until death or study termination.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

No additional data will be collected, and the final analyses for the clinical study report will be conducted, after all patients enrolled in the study have discontinued from the trial either because modakafusp alfa is discontinued or because patients remaining on treatment have been transferred to an open-label rollover study, a single-patient investigational new drug (IND), or any other regulated form to access an investigational drug (Section 6.3.5).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosure

Endpoint	Phase	Definition	Maximum Time Frame
Primary:			
Frequency and severity of TEAEs.	Phase 1b and phase 2 safety lead-in	Standard safety assessments.	Up to ~55 months.
Number of patients with DLTs.	Phase 1b and phase 2 safety lead-in	Standard safety assessments.	Up to ~55 months.
Number/percentage of patients with 1 or more SAEs.	Phase 1b and phase 2 safety lead-in	Standard safety assessments.	Up to ~55 months.
Number/percentage of patients with 1 or more TEAE leading to dose modifications and/or treatment discontinuation.	Phase 2 expansion	Standard safety assessments.	Up to ~55 months.
Secondary:			
MTD or PAD, if available.	Phase 1b	See Section 6.1.1.	During phase 1b.
RP2D.	Phase 1b and phase 2 safety lead-in	See Section 6.1.1	During phase 1b and phase 2 safety lead-in.
Frequency and severity of TEAEs according to the NCI CTCAE v5.0.	Phase 2 expansion	Standard safety assessments.	Up to ~55 months.
Number/percentage of patients with 1 or more SAEs.	Phase 2 expansion	Standard safety assessments.	Up to ~55 months.
Number/percentage of patients with 1 or more TEAE leading to dose modification and/or treatment discontinuation.	Phase 2 expansion	Standard safety assessments.	Up to ~55 months.
PK: C_{max}, t_{max}, AUC_t, AUC_∞, $t_{1/2z}$, CL, and V_{ss}	Phase 2 safety-lead in	Standard PK assessments	Dose escalation phase: C1D1-C1D4, C2D1-C2D4, and Day 1 of Cycles 3-6. Safety Lead-in phase: C1D1-C1D15, C3D1-C3D15, and Day 1 of Cycle 2/ Cycle 4-beyond.
ORR per RECIST v1.1.	Phase 1b	The proportion of patients who achieve CR or PR (determined by the investigator) during the study in response-evaluable population.	Up to ~55 months.
PFS per RECIST v1.1 for patients with solid tumors.	Phase 1b and phase 2	The time from the date of the first dose of study	Up to ~55 months.

Table 6.a Primary and Secondary Endpoints for Disclosure

Endpoint	Phase	Definition	Maximum Time Frame
		drug to the date of first documentation of PD according to RECIST v1.1 or death due to any cause, whichever occurs first.	
OS	Phase 1b and phase 2	The time from the date of first dose of study drug to the date of death due to any cause.	Up to ~55 months.
DCR	Phase 1b and phase 2	CR + PR + SD	Up to ~55 months.
DOR	Phase 1b and phase 2	The time from the date of first documentation of a PR or better to the date of first documentation of PD for responders (PR or better).	Up to ~55 months.
TTP	Phase 1b and phase 2	The time from the date of the date of the first dose of study drug to the date of first documentation of PD according to RECIST v1.1.	Up to ~55 months.
ORR, DCR, DOR, TTP, and PFS based on iRECIST.	Phase 2 expansion	See above.	Up to ~55 months.
Modakafusp alfa–induced Type I IFN gene expression signature in peripheral blood.	Phase 1b and phase 2	See Section 13.6.	Up to ~55 months.
Anti-modakafusp alfa antibody incidence and titer.	Phase 1b and phase 2	See Section 13.6.	Up to ~55 months.

AUC_t : area under the plasma concentration versus time curve from 0 to time t; CxDx: Cycle x Day x; CL: clearance; C_{max}: maximum observed concentration; CR: complete response; DCR: disease control rate; DOR: duration of response; DLT: dose-limiting toxicity; IFN: interferon; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, Version 1.1; ORR: overall response rate; OS; overall survival; PFS: progression-free survival; PK: pharmacokinetic(s); PR: partial response; RO: receptor occupancy; SAE: serious adverse event; SD: stable disease; $t_{1/2z}$: terminal disposition phase half-life; TEAE: treatment-emergent adverse event; t_{max}: time of first occurrence of C_{max}.

6.3.4 Total Study Duration

The estimated time frame for study completion is 55 months (12 months of enrollment in escalation, 18 months of enrollment in expansion, 24 months of treatment, and 1 month of follow-up).

6.3.5 Posttrial Access

At the end or termination of the study (Section 9.4), ongoing patients may continue to receive modakafusp alfa as a SA or in combination with pembrolizumab in an extension phase of this study or will be given the opportunity to enroll in a separate open-label rollover study, a single-patient IND, or other regulated access to continue receiving modakafusp alfa as a SA or in combination with pembrolizumab if, in the opinion of the investigator and confirmed by the sponsor, they have experienced a clinically important benefit from modakafusp alfa or in combination with pembrolizumab received in the study, have no alternative therapeutic option, and would be harmed without continued access. Patients may receive modakafusp alfa as a SA for up to 1 year or in combination with pembrolizumab for up to 2 years.

6.3.5.1 Duration of Posttrial Access

Continued access to modakafusp alfa will be terminated for individuals who are no longer benefitting from modakafusp alfa (eg, they have completed the recommended course of therapy or their disease has resolved), the benefit-risk no longer favors the individual, if modakafusp alfa becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of modakafusp alfa has been suspended or stopped by the sponsor, or modakafusp alfa can no longer be supplied.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Adult patients aged ≥18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
3. Life expectancy >12 weeks according to investigator's judgment.
4. Phase 1b dose escalation: Eligible patients must have histologically confirmed advanced (locoregionally recurrent, not amenable to curative therapy) or metastatic solid tumors.
5. Measurable disease per RECIST v1.1. At least 1 target lesion amenable for biopsy is required for enrollment in phase 1b. A minimum of 1 target lesion for response assessment is required for enrollment in phase 2. A separate lesion amenable for biopsy is required for enrollment in phase 2 for cohorts I and II post futility analysis and for all patients (safety lead-in and expansion) with subgroup III melanoma.
6. Phase 1b Dose Escalation: Patients with histologically confirmed advanced locally (locoregionally recurrent, not amenable to curative therapy) or metastatic solid tumors.

   Phase 2 Dose Expansion:

The combination cohorts, including patients in the safety-lead phase, will enroll patients with unresectable/metastatic melanoma in the following subgroups:

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

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

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

- Patients with BRAF V600E mutant melanoma may have received prior BRAF inhibitor therapy.
- For cohorts I and II, there is no limitation of total number of prior line(s) of therapy, but the number of prior line(s) containing anti-PD1 must be ≤2 in the metastatic setting.
- For the expansion cohort III, patients who received an anti-PD-1 treatment in the adjuvant setting must have completed that treatment at least 6 months prior to enrollment and must not have progressed on the anti-PD1 adjuvant treatment.
- Primary resistance is defined as a best response of PD or SD<6 months to an anti-PD1 alone or in combination with other agents (ie, CTLA4) in the initial anti-PD1 containing treatment.
- Acquired resistance is defined as a progression following a best response of CR, PR, or SD >6 months to a prior anti-PD1 alone or in combination with other agents (ie, CTLA4).

7. Reproductively female patients who:
   - Are postmenopausal for at least 2 years before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential (as defined in Section 9.3.9), due to unknown risks and potential harm to an unborn child/infant, must agree to the following:
     – Agree to practice 1 highly effective method of contraception (Section 8.9.1) and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 7 days after the last dose of modakafusp alfa or 4 months after the last dose of pembrolizumab, whichever is longer, OR
     – Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

  - Agree not to donate an egg or eggs (ova) or breastfeed a baby during the study and through 7 days after the last dose of modakafusp alfa or 4 months after the last dose of pembrolizumab, whichever is longer.

8. Reproductively male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception (Section 8.9.1) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab), OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
   - Agree not to donate sperm during the study and through 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab).
9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
    - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, platelet count $\geq 75.0 \times 10^9$/L, and hemoglobin ≥80 g/L without growth factor or transfusion support for ANC and platelets in the preceding 2 weeks.
    - Total bilirubin ≤1.5 times the upper limit of normal (ULN).
    - Serum alanine aminotransferase or aspartate aminotransferase ≤3.0 times the ULN (<5 times the ULN if liver enzyme elevations are due to liver metastases).
    - Creatinine <1.5 times the ULN or estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) (Levey et al. 2006) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey et al. 2009) equations.
11. Patients must agree to the applicable biopsy requirements as detailed in the SOE.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Treatment with any SoC or investigational anticancer drug within 28 days or 5 half-lives before administration of modakafusp alfa, whichever comes first. The washout period is 3 weeks for previous major surgery, 2 weeks for previous radical radiation (including chemoradiation and whole-brain radiation), and 5 days from last dose for focal radiation for symptomatic metastases.

2. Persistent toxicity from previous treatments that has not resolved to ≤CTCAE v.5 Grade 1 prior to administration of modakafusp alfa, except for alopecia, Grade 2 neuropathy, Grade 2 asthenia/fatigue, or autoimmune endocrinopathies with stable replacement therapy.
3. History of any of the following ≤6 months before the first dose of modakafusp alfa: New York Heart Association Grade III or IV congestive heart failure, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, any ongoing symptomatic cardiac arrhythmias Grade >2, pulmonary embolism, symptomatic cerebrovascular events, or any other serious cardiac condition (eg, symptomatic pericardial effusion or restrictive cardiomyopathy). Chronic, stable atrial fibrillation on stable anticoagulant therapy, including low molecular-weight heparin, is allowed.
4. Baseline QTcF >480 msec (Grade ≥2), history of congenital long QT syndrome, or torsades de pointes.
5. History of immune-related AEs related to treatment with prior anti-PD1/PD-L1 that required treatment discontinuation (phase 2).
6. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or has compromised ability to provide written informed consent.
7. History of uncontrolled brain metastasis or previously treated metastases receiving corticosteroid dose ≥20 mg/day of prednisone equivalent at the time of receiving the first dose of modakafusp alfa.

   Note: Patients with carcinomatosis meningitis or leptomeningeal disease are excluded, regardless of clinical stability.
8. Patients with uveal (ocular) or mucosal melanoma (phase 2).
9. Patients with acral lentiginous melanoma are excluded in phase 2 except for the safety lead-in phase.
10. Ongoing or active infection.
11. Known history of HIV infection or any other relevant congenital or acquired immunodeficiency.
12. Known hepatitis B (HBV) surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients with a positive HBV core antibody can be enrolled but must have an undetectable hepatitis B viral load.
13. Autoimmune disease requiring systemic immunosuppressive therapy. Patients with immune mediated endocrine deficiency from previous therapy with stable hormone replacement are exceptions.
14. History of severe allergic or anaphylactic reaction to recombinant proteins or excipients used in modakafusp alfa or pembrolizumab formulation.

15. Patients who are lactating and/or breastfeeding or have a positive urine or serum pregnancy test during the screening period.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

The initial dose should be based on a patient's weight at screening and only adjusted if there is a ≥10% change in body weight.

Investigational sites should refer to the pharmacy manual for preparation of each dose. Modakafusp alfa doses <1.5 mg/kg will be administered over 1 hour (±10 minutes). Modakafusp alfa doses ≥1.5 mg/kg will be administered over 2 hours (±10 minutes) and could be extended to 4 hours at the investigator's discretion. Any decrease in infusion duration must be discussed with and agreed upon by the sponsor. If a patient presents with an infusion-related reaction at any dose level, the duration of the infusion may be extended per investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of infusion must not exceed 7 hours.

In the combination treatment cohorts, the recommended pembrolizumab dose of 400 mg will be administered as an IV infusion over 30 ±10 minutes Q6W in combination with modakafusp alfa. Please see premedication and observation guidelines in Section 8.8.1.

Pembrolizumab will be administered before modakafusp alfa on days when both modakafusp alfa and pembrolizumab are given. At least 30 minutes should elapse between the completion of the infusion of the first study drug and the initiation of the infusion of the second study drug.

8.2 Definitions of Dose-Limiting Toxicities

Toxicity will be evaluated according to the NCI CTCAE v 5. A DLT is defined as any of the following AEs that occur in the escalation phase or in the combination safety lead-in phase during Cycle 1 unless they are considered by the investigator to be clearly unrelated to therapy with modakafusp alfa.

- Any Grade 5 TEAE.
- Febrile neutropenia: Grade ≥3 neutropenia (ANC $<1.0 \times 10^9$/L) with fever and/or infection, where fever is defined as a single temperature >38.3°C or sustained temperature of ≥38°C for more than 1 hour.
- Grade 4 neutropenia lasting >7 days.
- Grade 4 thrombocytopenia lasting more than 7 consecutive days, or if platelet transfusion is required, or if Grade ≥2 bleeding happens at any moment. A platelet count $<10 \times 10^9$/L at any time is a DLT.

- Grade ≥3 thrombocytopenia lasting longer than 14 days or accompanied by Grade ≥2 bleeding.
- **Any Grade 3 immune-related AEs such as pericarditis, pneumonitis, cardiotoxicity, hepatitis, or neurotoxicity.**
- Delay in the initiation of Cycle 2 by more than 14 days from the calculated start date due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
- Any Grade ≥3 nonhematologic toxicity **with the following exceptions**:
  - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week.
  - Grade 3 fatigue that lasts <3 days.
  - Grade 3 endocrine disorder that is managed with or without therapy and the patient is asymptomatic.
  - Grade 3 or 4 inflammatory reaction attributed to a local antitumor response.
  - Grade 3 or 4 asymptomatic laboratory changes (other than renal and hepatic laboratory values) that can be successfully corrected (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
  - Isolated Grade 3 elevation of ALT and/or AST that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 nausea and/or emesis that can be controlled to Grade <3 in ≤3 days with the use of optimal antiemetics (defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Grade 3 rash and pruritis that respond to a standard treatment and resolve or improve to Grade <3 within 7 days.
  - Grade 3 diarrhea that can be controlled to Grade <3 in ≤3 days with appropriate treatment.
  - Any other Grade 3 TEAE for which NCI CTCAE v5 Grade 4 or 5 does not exist or the NCI CTCAE does not consider the AE Grade 4 to be life-threatening.
- Any Grade 2 nonhematologic toxicity that is considered by the investigator to be related to study drug and dose-limiting.

In the dose escalation phase, DLTs are defined as events meeting the criteria above that occur before Cycle 2 Day 1 administration. TEAEs meeting DLT definitions occurring in later cycles or during expansion will determine the suitability of the MTD as the RP2D.

8.3 Phase 1b Modakafusp Alfa SA Dose Escalation Schema

The 2-parameter BLRM implementing the EWOC principle 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 E) will be used to inform dose escalation decisions and MTD estimation, along with consideration of other emerging safety, clinical, PK, and pharmacodynamic data. Doses will be escalated as shown in Table 8.a.

Table 8.a Planned Dose Levels

Dose Level	Dose (Unit)
–1	0.05 mg/kg
1	0.1 mg/kg
2	0.2 mg/kg
3	0.4 mg/kg
4	0.75 mg/kg
5	1.5 mg/kg
6	3.0 mg/kg
7	6.0 mg/kg

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
- At least 9 patients are enrolled at the next recommended dose, 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, the 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 E.

8.4 Phase 2 Modakafusp Alfa Dose Expansion

A minimum of 3 patients will be enrolled at the modakafusp alfa RP2D in combination with pembrolizumab 400 mg Q6W to evaluate safety and tolerability in a single safety lead-in phase. The safety lead-in phase will start with the enrollment of 3 initial patients to evaluate the tolerability during the Cycle 1 DLT evaluation period of modakafusp alfa 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 Q6W, the combination dose and regimen could be selected for the 3 melanoma disease cohorts.

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 (ie, 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 in the first dose cohort. 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. Subsequent cohorts, if any, will not require staggering between patients.

8.5 Additional Safety Stopping Rules

Patients will be monitored continuously for safety. Circumstances that may warrant enrollment hold include the following:

- Fatal Events:
  - A threshold for related fatal AEs of 6% is proposed for the whole trial (dose escalation plus expansions). If this mark is passed during the expansion phase, enrollment will be halted, and the safety of the dose selected will be re-evaluated.
  - During dose escalation, enrollment will be stopped if ≥2 related Grade 5 AEs happen in the first 12 (16%) patients or if ≥3 (10%) events happen in 30 patients. If escalation goes beyond 30 patients, the 6% mortality threshold will be used.
- Nonfatal Events:
  - In escalation phase, dose escalation rules based on DLTs and guided by BLRM will be implemented.
  - Additionally, Grade 4 life-threatening, related, nonhematologic AEs must stay <10% during the trial once 30 patients have been dosed.

In these circumstances, the final decision about trial execution will be made after a full review of the safety data by the sponsor and the Safety Management Team.

8.6 Dose Modification Guidelines

8.6.1 Intrapatient Dose Escalation

Patients who have tolerated treatment with modakafusp alfa well at the initially assigned dose may be allowed to increase their doses of modakafusp alfa in subsequent cycles of treatment following sponsor and investigator review of the available data. Intrapatient dose escalation will be permitted only after all patients in the next higher dose level cohort have completed assessments for Cycle 1 and a decision has been made that this dose level does not exceed the MTD.

8.6.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

To begin a new cycle of treatment with either modakafusp alfa alone or in combination with pembrolizumab, the patient must meet the following criteria:

- ANC must be ≥1000/mm^3. Granulocyte-colony stimulating factor (G-CSF) can be used to reach this level.
- Platelet count must be ≥50,000/mm^3 without transfusion support.

For therapy to resume, toxicity considered to be related to treatment with modakafusp alfa must have resolved to Grade ≤1 or baseline (Grade ≤2 for platelets and neutrophils), or to a level considered acceptable by the physician. If the patient does not meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for retreatment criteria have been met.

If a subsequent cycle is delayed more than 14 days because of a related AE, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor. Modakafusp alfa dosing may be continued at the previously established safe dose level or below.

8.6.3 Criteria for Treatment Interruption and Dose Reduction

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol.

8.6.3.1 Modakafusp Alfa Dose Modification Guidelines

Table 8.b provides general dose modification recommendations for modakafusp alfa. When the dose of modakafusp alfa is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. If there are transient laboratory abnormalities that, based on investigator assessment, are not clinically significant, continuation of therapy without dose modification is permissible upon discussion with the sponsor. See details for managing specific AEs in Section 8.10.

Table 8.b Dose Modification Recommendations for Toxicities Possibly Related to Modakafusp Alfa

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline and then restarted at the same dose or, depending on the toxicity, at the previous safe dose level or below.
Grade 3, Grade 4 (not life-threatening per seriousness criteria), and Grade 4 asymptomatic laboratory AEs	Hold modakafusp alfa until resolution to Grade ≤1 or baseline, and then resume treatment at a reduced dose level. In case of Grade 3 hematological toxicity (anemia, thrombocytopenia, neutropenia, or lymphopenia) or Grade 3 asymptomatic laboratory AEs, the patient can continue at the same dose or a reduced dose at the investigator's discretion.
Grade 4 (life-threatening per seriousness criteria) AEs	Permanently withdraw the patient from the study.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment can be resumed at a reduced dose level after resolution of AEs to Grade ≤1 or baseline.

AE: adverse event.

When a dose reduction occurs, the modakafusp alfa dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of modakafusp alfa can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. If more than 2 dose reductions are required for the same AE, the patient should be discontinued from therapy.

8.6.3.2 Pembrolizumab Dose Modification Guidelines

In this study, the dose of pembrolizumab cannot be modified. Depending on the toxicity observed, the infusion of pembrolizumab can be interrupted (in case of IRR, for example), delayed, or discontinued. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted, but dose modifications are not allowed. The patient should be treated according to the appropriate standard of care. Patients who discontinue pembrolizumab for reasons described in the pembrolizumab label other than irAEs may continue modakafusp alfa treatment.

General instructions:

1. It is recommended that the management of irAEs follow NCCN (NCCN 2021) or SITC (Puzanov et al. 2017) guidance. If pembrolizumab has been withheld, it can be resumed after the AE severity has decreased to Grade 1 or baseline level and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if the AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
2. For severe and life-threatening irAEs, IV corticosteroid treatment should be initiated first followed by oral steroid therapy. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Pembrolizumab dose modification guidelines for irAEs are detailed in Table 8.c.

Table 8.c Pembrolizumab Dose Modification Guidelines for irAEs

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab
Pneumonitis	Grade 2	Withhold.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue.
Diarrhea/colitis	Grade 2 or 3	Withhold.
	Grade 4	Permanently discontinue.
AST/ALT elevation or increased bilirubin	Grade 2	Withhold.
	Grade 3 or 4	Permanently discontinue.
Type 1 diabetes mellitus or hyperglycemia	New onset type 1 diabetes mellitus or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold.
Hypophysitis	Grade 2	Withhold.
	Grade 3 or 4	Withhold or permanently discontinue.[a]
Hyperthyroidism	Grade 2	Continue.
	Grade 3 or 4	Withhold or permanently discontinue.
Hypothyroidism	Grade 2 to 4	Continue.
Nephritis and renal dysfunction	Grade 2	Withhold.
	Grade 3 or 4	Permanently discontinue.
Myocarditis	Grade 1 or 2	Withhold.
	Grade 3 or 4	Permanently discontinue.

Table 8.c Pembrolizumab Dose Modification Guidelines for irAEs

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include, but are not limited to, Guillain-Barre Syndrome and encephalitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; GI: gastrointestinal; irAE: immune-related adverse event; IV: intravenous.
[a] Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.
For patients with Grade 3 or 4 immune-related endocrinopathy that does not require withholding of pembrolizumab, pembrolizumab may be resumed when the AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy or metabolic control has been achieved (in case of type 1 diabetes mellitus).

8.6.4 Criteria for Discontinuing of Treatment with Study Drugs

Patients should discontinue treatment with either modakafusp alfa or pembrolizumab, or both, if they meet any of the criteria listed below. Patients who discontinue pembrolizumab for reasons other than irAEs may continue modakafusp alfa treatment as a single agent if modakafusp alfa discontinuation criteria are not met; patients who discontinue modakafusp alfa may continue pembrolizumab as a single agent if pembrolizumab discontinuation criteria are not met. In the event of discontinuation of study therapy (modakafusp alfa and pembrolizumab), patients will undergo the end of treatment (EOT) visit.

8.6.4.1 Criteria for Discontinuing Modakafusp Alfa

Study drug **must** be permanently discontinued if any of the following criteria are met:

1. Patient experiences an AE in Cycle 1 meeting criteria for a DLT that is considered life-threatening.
2. Confirmed progressive disease according to RECIST v1.1.
3. Start of new/subsequent anticancer treatment.
4. Confirmed pregnancy.
5. Patient meets any of the criteria for discontinuation specified in Section 8.10.

Study drug **may** be discontinued after discussion with the study sponsor, if any of the following criteria are met:

1. Any non-life-threatening AEs if the investigator determines that study continuation is no longer in the patient's best interest.
2. Any AE that changes the benefit-risk assessment for a patient.

3. Clinical deterioration of the patient as assessed by the investigator.
4. CR.
5. Unsatisfactory therapeutic response.
6. Study terminated by sponsor.
7. Withdrawal by subject.
8. Subject's death.
9. Lost to follow-up.
10. Delay of next cycle by more than 14 days.
11. Important protocol deviations from inclusion/exclusion criteria.

If treatment is discontinued, the EOT visit should be completed within 30 to 40 days after the last administration of modakafusp alfa.

8.6.4.2 Criteria for Discontinuing Pembrolizumab

Pembrolizumab will be discontinued if any of the criteria described in Table 8.c or the pembrolizumab SmPC have been met. Additionally, pembrolizumab may be discontinued for other reasons if it is considered in the best interest of the patient and discussed with the medical monitor.

Permanently discontinue pembrolizumab for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy).
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity.
- Grade 3 or 4 nephritis.
- Grade 4 severe skin reactions or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis.
- AST or ALT greater than 5 × ULN or total bilirubin greater than 3 × ULN.
  - For patients with liver metastases who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week.
- Grade 3 or 4 IRRs.
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of an irAE.
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade ≤1 within 12 weeks after last dose of pembrolizumab.

- Any severe or Grade 3 treatment-related AE that recurs.

8.7 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Radical radiation or extended field radiation therapy for disease under study. Local radiotherapy for localized painful metastases or at risk of producing complications is permitted after agreement with the sponsor's medical monitor.
- Any other anticancer treatment or investigational agent other than modakafusp alfa, including agents that are commercially available for indications other than the disease under study that are being investigated for the treatment of the disease under study.
- Concomitant chronic corticosteroid administration of >20 mg/day of prednisone or equivalent unless given as premedication prior to administration of modakafusp alfa to prevent onset and severity of IRRs, as premedication prior to administration of certain blood products or for exacerbations of respiratory tract disorders, acute pain management, suspected or confirmed immune-mediated thrombocytopenia, immune-related AEs, or if tumor flare is suspected.

8.8 Permitted Concomitant Medications and Procedures

8.8.1 Premedication

Due to the occurrence of Grade 2 IRRs in 8 of 17 patients receiving modakafusp alfa at doses of 0.1 to 1.5 mg/kg Q3W in the current study as of the data cutoff of 23 January 2021, the following list of medications are mandatory in all cycles before infusion of modakafusp alfa to prevent and/or mitigate this potential AE.

1. Corticosteroid IV or orally (PO) (dexamethasone 10 mg to 20 mg or equivalent) 60 minutes to 2 hours before treatment.
2. Acetaminophen 650 mg to 1000 mg PO 60 minutes to 2 hours before treatment.
3. Diphenhydramine or equivalent 25 mg to 50 mg PO approximately 1 hour before treatment.

Montelukast may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is ineffective. Additional premedications of nonsteroidal anti-inflammatory drugs (NSAIDs) and H_2 blockers could be added per investigator's discretion.

Medication(s) shall be administered according to medical standards and at sufficient time prior to start of infusion of modakafusp alfa that allows the premedication drugs to exert their effects.

For the phase 2 expansion phase, the history of IRR to prior CPI treatment will be collected.

During the infusion and for 6 hours post-infusion in the first 2 treatment cycles, patients should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage IRRs. In Cycle 3 and beyond, patients should be continually monitored for at least 2 hours post the end of infusion, and the monitoring duration could be extended per a

patient's prior dosing experience. Potential IRRs shall be managed as medically indicated including, but not limited to, repeated administration of drugs described above.

For details about treatment of IRRs, please refer to Section 8.10.1. Procedures for reporting AESIs are described in Section 10.2.1.

8.8.2 Postinfusion Medication

Patients may receive concomitant medications on the first and second days after all infusions per institutional protocols.

8.8.3 Other Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients as medically indicated. All blood products and concomitant medications will be recorded in the electronic case report forms (eCRFs, which refers to any media used to collect study data whether paper or electronic) as specified in the SOE (Appendix A).

The use of G-CSF and/or platelet transfusions is prohibited during the DLT evaluation period of the escalation phase (Cycle 1) unless deemed medically indicated by the investigator.

The following medications and procedures are permitted while the patient is receiving the study drug:

- Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their general use should follow the product label, published guidelines, and institutional practice. [redacted]
- Patients should be transfused with RBCs and platelets as clinically indicated. Transfusions must be recorded in the concomitant procedure pages of the eCRF.
- Concomitant treatment with bisphosphonates will be encouraged for all patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice Guidelines or institutional practice in accordance with the product label, unless specifically contraindicated. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.
- Topical or inhaled steroids (eg, for the treatment of asthma) are permitted.
- Systemic steroids for acute management of pain, suspected or confirmed immune-mediated thrombocytopenia or other disease or treatment-related complications are permitted.
- Intravenous immunoglobulins (IVIG) usage is acceptable for prolonged Grade 4 transfusion-dependent thrombocytopenia or other investigator criteria if it is considered that there is an underlying autoimmune mechanism.

- Thrombopoietin agonists are allowed for thrombocytopenia management at investigator's discretion.
- Vaccinations to prevent COVID-19 viral infections and other infections (eg, influenza, pneumococcus) are allowed at the investigator's discretion with the following considerations:
  1. Live vaccines are not recommended.
  2. Vaccination and modakafusp alfa dosing on the same day is not recommended.
  3. For patients in the dose escalation, vaccination in the Cycle 1 DLT evaluation period is not recommended.

Supportive measures consistent with optimal patient care may be given throughout the study.

8.9 Precautions and Restrictions

An interference with serological testing has been described with the anti-CD38 antibody daratumumab. Daratumumab binds to CD38 on RBCs and results in a positive indirect antiglobulin test (indirect Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not affected. Type and screen patients before starting modakafusp alfa if this was not performed previously.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

8.9.1 Contraception and Pregnancy Avoidance Procedures

It is not known what effects modakafusp alfa has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or impregnating a partner. Patients of reproductive potential should use effective methods of contraception through defined periods during and after study treatment as specified below. Patients must also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

Reproductively female patients must meet one of the following:

- Postmenopausal for at least 2 years before the screening visit OR
- Surgically sterile, OR
- If they are of childbearing potential (as defined in Section 9.3.9), due to unknown risks and potential harm to an unborn child/infant, must agree to the following:
  – Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time (Table 8.d) from the time of signing the informed consent

through 7 days after the last dose of modakafusp alfa or 4 months after the last dose of pembrolizumab, whichever is longer OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate an egg or eggs (ova) or breastfeed a baby during the study through 7 days after the last dose of modakafusp alfa or 4 months after the last dose of pembrolizumab, whichever is longer.

Reproductively male patients, even if surgically sterilized (ie, status postvasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception (Table 8.d) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab) OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the study and for 7 days after the last dose of modakafusp alfa (no restriction for pembrolizumab).

Table 8.d Highly Effective Methods of Contraception

Highly Effective Methods	Additional Effective (Barrier) Methods
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation	Male or female condom with or without spermicide (female and male condoms should not be used together)
Oral	
Intravaginal	
Transdermal	
Progestogen-only hormonal contraception associated with inhibition of ovulation	
Oral	
Injectable	
Implantable	
Intrauterine device	Cap, diaphragm, or sponge with spermicide
Intrauterine hormone-releasing system	
Bilateral tubal occlusion	
Vasectomized partner	
Sexual abstinence	

8.10 Management of Specific Adverse Reactions

8.10.1 Infusion-Related Reactions

An IRR can develop during or shortly after administration of a drug. Signs and symptoms may include pruritus, urticaria, fever, rigors/chills, diaphoresis, bronchospasms, and cardiovascular collapse. In modakafusp alfa studies, IRRs are designated as AESIs.

Premedication is detailed in Section 8.8.1. Patients should be carefully monitored during modakafusp alfa infusions. Trained trial staff at the clinic should be prepared to intervene in case of any IRRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

Patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion.

Post-medication may be considered at the investigator's discretion, as medically indicated, and per Section 8.8.2.

In case of an infusion reaction, serum samples should be taken for central evaluation of immunogenicity and circulating biomarkers (Appendix A). These blood draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

All AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's seriousness or causal relationship as described in Section 10.2.1. When recording IRRs in the eCRF, the signs and symptoms should be recorded and should be marked as an AESI.

8.10.1.1 IRRs After Modakafusp Alfa Dosing

The recommendations for managing IRRs related to modakafusp alfa are presented in Table 8.e and Table 8.f.

Table 8.e Recommendations for Managing Grade 1 and Grade 2 IRRs

IRR	Action
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. Consider pre- and postmedication before restarting the infusion and for future modakafusp alfa administrations.
Grade 2 event of laryngeal edema, or Grade 2 event of bronchospasm that does not respond to systemic therapy.	Patient must be withdrawn from treatment if the event does not resolve within 6 hours from onset.

Table 8.f Recommendations for Managing Grade ≥3 IRRs

IRR	Action
Any Grade 4 life-threatening event:	Patient must be withdrawn from treatment.
Grade 3 bronchospasm or laryngeal edema:	Patient must be withdrawn from treatment.
Grade 3 events other than bronchospasm or laryngeal edema:	Infusion must be stopped, and the patient must be observed carefully until resolution of the IRR.
If the intensity of the IRR remains at Grade 3 after 2 hours:	Patient must be withdrawn from treatment.
If the intensity of the IRR decreases to Grades 1 or 2:	Infusion may be restarted at the investigator's discretion. Administer corticosteroids, acetaminophen, and antihistamines per Sections 8.8.1 and 8.8.2 before restarting infusion. Within 2 hours upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
If the intensity of the IRR returns to Grade 3:	The procedure described above may be repeated after restart of the infusion at the investigator's discretion.
If the intensity of the IRR increases to Grade 3 for a third time:	Patient must be withdrawn from treatment.

IRR: infusion-related reaction.

8.10.1.2 IRRs After Pembrolizumab Dosing

Patients with Grade 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring. For Grade 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued.

8.10.2 Low Platelet Counts

Treatment decisions will be based on a patient's platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled infusions to be postponed or to be permanently discontinued. If at any time the platelet count is less than 10×10^9/L, or if the patient shows a bleeding tendency considered to be due to thrombocytopenia occurring after initiation of modakafusp alfa treatment, the patient should be withdrawn from modakafusp alfa treatment unless clinical benefit is observed and the investigator considers that thrombocytopenia can be managed with dose modifications. The investigator can consider the usage of corticosteroids, IVIG or thrombopoietin agonists in selected cases depending on severity, duration, transfusion requirements, and additional risk factors for bleeding and based on the suspected underlying mechanism. Platelet transfusion and close monitoring of platelet counts should follow institutional guidelines.

8.10.3 Management of Immune-Mediated Adverse Events

Pembrolizumab can cause pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin adverse reactions, IRRs, and other immune-mediated AEs. Monitoring of these AEs is required in both the safety lead-in and expansion cohorts in the combination arm. Patients with AEs that are suspected to be related to pembrolizumab should be evaluated by appropriate methods, including physical examinations, laboratory tests, and imaging. These irAEs will be treated based on standard of care, local institutional guidance, the WARNINGS AND PRECAUTIONS section of the package insert, and the proper use guidance of pembrolizumab. It is recommended that the management of irAEs follow NCCN (NCCN 2021) or SITC (Puzanov et al. 2017) guidance.

8.11 Blinding and Unblinding

This is an open-label study.

8.12 Description of Investigational Agents

Modakafusp alfa is a humanized anti-CD38, IgG4, mAb fused to an attenuated IFN-α2b. The initial frozen liquid modakafusp alfa formulation is used for all phase 1b dose escalation patients. The redeveloped lyophilized modakafusp alfa formulation is to be used in dosing phase 2 patients. Additional details can be found in the modakafusp alfa IB.

Pembrolizumab solution for infusion consists of 100 mg/4 mL (25 mg/mL) in a single-dose vial or powder for solution for infusion 50 mg (1 vial contains 50 mg pembrolizumab). Please refer to the pharmacy manual and the most recent pembrolizumab SmPC for details.

8.13 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container permit.

8.13.1 Modakafusp Alfa

Modakafusp alfa is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling modakafusp alfa. Detailed information is available in the IB and pharmacy manual.

8.13.2 Pembrolizumab

Please refer to the most recent SmPC for preparation, reconstitution, and administration instructions.

A commercially available IV formulation of pembrolizumab background therapy will be used. In countries or study centers where pembrolizumab is designated a noninvestigational product, sites will be expected to source this commercially available product through their local hospital pharmacy or licensed distributor. In countries or centers where pembrolizumab is designated as an investigational product, sites will have pembrolizumab supplied and packaged by the sponsor. This supply will be labeled appropriately for investigational use as per the regulations of the relevant country health authority.

8.14 Packaging and Labeling

Supplies of modakafusp alfa and pembrolizumab will be labeled according to the current ICH guidelines on GCP and Good Manufacturing Practice and will include any locally required statements.

8.15 Storage, Handling, and Accountability

8.15.1 Modakafusp Alfa

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all modakafusp alfa received and that any discrepancies are reported and resolved before use of modakafusp alfa.

Temperature conditions for modakafusp alfa, a list of ancillary supplies approved for use with modakafusp alfa, and thawing or reconstitution and dilution procedures for modakafusp alfa vials are provided in the pharmacy manual.

Each modakafusp alfa shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

The investigator is responsible for ensuring that deliveries of modakafusp alfa and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive modakafusp alfa, and only authorized staff at the investigational center may supply or administer modakafusp alfa. All modakafusp alfa must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator, institution, or head of the medical institution (where applicable) is responsible for modakafusp alfa accountability, reconciliation, and record maintenance (eg, receipt, reconciliation, and final disposition records).

A record of modakafusp alfa accountability (modakafusp alfa and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused modakafusp alfa will be disposed of, retained, or returned to the sponsor or designee.

Further guidance and information are provided in the pharmacy manual.

8.15.2 Pembrolizumab

Pembrolizumab must be stored in a secure, limited-access location, according to conditions specified on the drug label. The investigator or designee must confirm that appropriate temperature conditions have been maintained and that any discrepancies are reported and resolved before use. Refer to the pharmacy manual and/or the most recent SmPC for additional details.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the internal review board (IRB)/independent ethics committee (IEC).

9.3 Study Procedures

Sites will make every effort to see patients in the clinic to complete all study-specified assessments as outlined in the SOE (Appendix A). In unavoidable circumstances, such as the COVID-19 public health emergency, exceptions can be made for alternative methods for conducting patient visits

and performing laboratory and imaging assessments as detailed below. Remote visits and telemedicine must comply with national and local laws and regulations. Such instances will be documented in the study records and electronic case report form (eCRF) if applicable, and the sponsor will be informed.

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. Evaluations during the screening period are to be conducted within 21 days before administration of the first dose of the study drug. Some procedures conducted during the screening period that are performed within 4 days of C1D1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified.

9.3.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

If necessary, informed consent may be obtained from a potential or current trial participant via electronic informed consent capabilities or an electronic face-to-face consent interview when these individuals are unable to travel to the site.

9.3.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.3.3 Medical History

During the screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it and the best response achieved by each one. Available key pathology and genomic biomarkers previously obtained from patient's tumor should be collected. In the phase 2 expansion, a patient's history of IRR to prior CPI therapy will be collected.

In addition, concomitant medications will be recorded as specified in Section 9.3.10.

The most recent prescreening diagnostic-quality computed tomography (CT) and/or magnetic resonance imaging (MRI) scans acquired for disease assessment, if available, should be submitted to the imaging core laboratory vendor for storage and for potential retrospective central reading. (refer to Section 9.3.14.2). The date of the scan(s) should be indicated. Availability of prescreening scan(s) is not a prerequisite for study eligibility.

9.3.4 Physical Examination

A physical examination will be performed (complete or symptom-directed) per standard of care at the times specified in the Schedule of Events (Appendix A).

If an investigator considers it safe and appropriate for a subject to miss a protocol-specified physical examination for COVID-19-related reasons, the study site physician or other qualified site staff will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) to assess subject safety and overall clinical status with a plan for in-person

evaluation if signs and symptoms warrant. Such instances will be documented in the study records and electronic case report form (eCRF) if applicable, and the sponsor will be informed.

9.3.5 Patient Height

Patient height will be measured during the screening visit only.

9.3.6 Patient Weight

Patient weight will be measured at the times specified in Appendix A. Initial dose should only be adjusted for a ≥10% change in body weight (Section 8.1).

9.3.7 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and oxygen saturation. They include also supine, semirecumbent, or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position; all subsequent measurements should be performed in the same initial position). Vital signs will be measured at the times specified in Appendix A.

Blood pressure will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any moment if the patient complains of symptoms consistent with IRR. If the patient experiences hypotension (with or without symptoms) intensive blood pressure monitoring according to local practice should be instituted. The patient cannot be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Any vital sign value that is judged by the investigator as clinically significant will be recorded both in the source documentation and the eCRF as an AE and monitored as described in Section 10.2.

9.3.8 ECOG Performance Status

ECOG performance status (Oken et al. 1982) will be evaluated at the times specified in Appendix A.

9.3.9 Pregnancy Testing

Pregnancy tests will be measured at the times specified in Appendix A. A serum or urine pregnancy test will be performed for patients of childbearing potential with negative results during screening, and again at C1D1 (baseline) if the screening test was performed more than 72 hours before the C1D1 dosing. A serum or urine pregnancy test must be performed predose (within 72 hours prior to dosing) on Day 1 of each cycle with negative results available before modakafusp alfa is administered. A serum or urine pregnancy test is required at EOT.

A patient of childbearing potential is defined as a patient with a uterus/ovary(ies) who (1) has not undergone a hysterectomy or bilateral oophorectomy or (2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses any time in the preceding 24 consecutive months).

9.3.10 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had from signing of the ICF through 30 days after the last dose of modakafusp alfa or the start of subsequent systemic anticancer therapy, whichever occurs first, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures (including any transfusion, tumor biopsies) completed by the patient will be recorded in the eCRF. See Sections 8.7 and Section 8.8 for a list of medications and therapies that are prohibited or allowed during the study.

9.3.11 TEAEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in Appendix A. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.3.12 ECG

12-lead ECG measurements will be performed at the time points specified in Appendix A. A qualified person will interpret the ECG. Triplicate ECGs will be read centrally. Single ECGs will be read locally.

Any ECG finding that is judged by the investigator as clinically significant will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. When the timing of ECG or vital sign measurements coincide with the timing of a blood draw (eg, PK sample), the ECG measurements and vital sign measurements should be completed first, followed by blood sampling.

During the dose escalation phase and safety lead-in of the phase 2 expansion, triplicate ECGs for initial heart rate-corrected QT interval evaluation and other parameters will be recorded on ECG recorders and electronically stored. These timepoints correspond with PK draws. Please refer to the PK sampling schedules (Table 16.f and Table 16.g). The ECG recorders will be provided by the ECG vendor. The provided recorders should have the capability to transmit ECG recording to the site computers so that ECGs are available for local safety assessment on-site by investigators.

The ECG measurements should be completed before the PK/pharmacodynamic blood draw. See Appendix B for food and beverage intake instructions.

9.3.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed either locally or centrally as indicated in each section.

In extenuating circumstances, such as during the COVID-19 public health emergency, laboratories closer to a patient's home may be utilized for local clinical laboratory assessments provided that pertinent laboratory information, including normal reference ranges, are provided to the sponsor or

designee. Central laboratory assessments must still be obtained at the site as needed and sent to sponsor-designated laboratories.

Handling of central clinical laboratory blood samples will be outlined in the Laboratory Manual. Immunoprofiling (mass cytometric analysis of T, B, and NK lymphocyte subsets), CD38 occupancy/density, biomarker testing (cytokine and chemokine panel), RNA sequencing, T-cell and B-cell receptor sequencing, modakafusp alfa concentrations for PK analysis, and immunogenicity testing (ADAs) are to be performed centrally. Decisions regarding eligibility for this study may be made using local laboratory determinations. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.3.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in Appendix A. They will be performed locally only.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Chemistry**	
Hematocrit	Albumin	Glucose (nonfasting)
Hemoglobin	Alkaline phosphatase	HCO_3 or CO_2
Platelet count	ALT	Total protein
WBC count	AST	LDH
WBC differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)	Bilirubin (total)	Phosphate
	Blood type [b]	Potassium
Coagulation:	Blood urea nitrogen	Sodium
aPTT	Calcium	Standard C-reactive protein
PT	Chloride	Urate or uric acid
Other	Creatinine	
TBNK assay (T cells [including CD4+ and CD8+ T cells], B cells, and NK cells) [a]		

ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; NK: natural killer; PT: prothrombin time; TBNK: quantification of T cells [including CD4+ and CD8+ T cells], B cells, and NK cells; WBC: white blood cell.
[a] Local analysis if available.
[b] A sample for blood typing to be taken only at baseline. If applicable, blood banks need to be alerted that the patient is going to receive an anti-CD38 antibody that may interfere with blood typing in a manner similar to daratumumab. If the blood bank issues a compatibility card, it should be made available to the patient. The patient needs to tell other healthcare providers that he/she is receiving an anti-CD38 antibody if, for example, a blood transfusion is needed.

If GFR is to be estimated, the MDRD (Levey et al. 2006) or CKD-EPI (Levey et al. 2009) equations shall be used.

Table 9.b Clinical Urinalysis Tests

Urinalysis		
Bilirubin	Nitrite	Specific gravity
Glucose	Occult blood	Turbidity and color
Ketones	pH	Urobilinogen
Leukocytes	Protein	

9.3.13.2 TBNK

Blood samples will be collected to measure absolute counts of T cells (including CD4+ and CD8+ T cells), B cells, and natural killer cells (TBNK) found within blood at various time points while the patient is on study (Table 9.a). Samples will be collected predose and analysis will be performed locally only if it is available at the site as specified in Appendix A for patients enrolled within phase 1b dose escalation.

9.3.13.3 Immunosafety Markers

Blood samples for the analysis of immunosafety for patients in pembrolizumab combination cohorts are shown in Table 9.c. These tests will be obtained as specified in the SOE Appendix A and performed locally only.

Table 9.c Immunosafety Laboratory Tests

Serum Chemistry		
Thyroid-stimulating hormone (TSH)	Free thyroxine (T4)	Cortisol (morning preferred)

9.3.14 Disease Assessment

At screening, CT and/or MRI scans will be performed unless chest, abdominal cavity, and pelvis diagnostic quality scans were performed within 5 weeks before the planned first dose of study drug. CT and/or MRI scans of the chest, abdominal cavity, and pelvis should be acquired with at least IV contrast. The imaging modalities used for a patient should remain consistent throughout the study. If IV contrast–enhanced CT scans are contraindicated for a particular patient, a noncontrast-enhanced CT of the chest should be acquired in addition to an oral contrast–enhanced CT of the abdomen and IV contrast–enhanced pelvic MRI.

At present, low-dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based

RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Repeat CT and/or MRI scans should be performed every 6 weeks through Cycle 6 and every 9 weeks thereafter, and as clinically indicated.

Response assessment will be calendar-based regardless of treatment delays/interruptions. Investigator assessment of disease response and progression will be based on RECIST v1.1 (Section 9.3.14.1) and iRECIST (Seymour et al. 2017) (phase 2 expansion only). Screening and on-treatment images, when available, should be submitted to the imaging core laboratory vendor for storage and potential retrospective central reading.

In extenuating circumstances, such as during the COVID-19 public health emergency, patients may use an alternative site for imaging with prior notification to the sponsor or designee.

9.3.14.1 RECIST v1.1 and Treatment Beyond Progression

Because treatment decisions will be made based on local assessment by the investigator, when assessing response, special consideration should be given to the tumor response characteristics associated with immunotherapy:

1. Measurable tumor size reduction may require a longer treatment duration with immunotherapy than with a cytotoxic regimen.
2. Although a rare event, response to immunotherapy may occur after appearance of PD, as assessed per conventional RECIST v1.1. In particular, small, new lesions may appear in the presence of other responsive target lesions (pseudoprogression).
3. Durable SD may represent antitumor activity of immunotherapy.

Therefore, RECIST v1.1 (Eisenhauer et al. 2009) will be implemented in this study as described below.

Contemporary immunotherapy protocols generally allow patients to continue treatment beyond initial radiographic evidence of progressive disease following further investigation, as accumulating data indicate it is possible that some patients treated with immunotherapy may derive clinical benefit beyond initial RECIST-defined progressive disease, which may not be captured by radiographic assessments. Therefore, despite an initial RECIST-defined PD, patients who are clinically stable and deriving benefit may remain on study until PD has been confirmed in subsequent imaging assessments. In this study, patients treated with modakafusp alfa will be permitted to continue treatment beyond initial RECIST v1.1-defined progressive disease if the following criteria are met:

1. Investigator-assessed overall clinical benefit from continued treatment with modakafusp alfa. The assessment of clinical benefit should consider whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

2. Tolerance of study drug(s).
3. Stable performance status.
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of progressive disease (eg, central nervous system [CNS] metastases).
5. Patient agrees to receive additional modakafusp alfa by signing a separate ICF informing of pseudoprogression and the potential risks and benefits of continuing treatment in these circumstances.

The decision to continue treatment beyond initial RECIST v1.1-defined progression should be discussed with the medical monitor and documented in the study records. Such patients may remain on the study and continue to receive monitoring according to the protocol-defined SOEs. Any additional post-RECIST v1.1 progression imaging time points acquired in patients that are considered clinically stable should also be collected and when available, submitted to the imaging core laboratory vendor for storage and potential, retrospective central reading. In general, treatment should be discontinued permanently either upon unequivocal evidence of further progressive disease based on subsequent imaging assessment or upon investigator's assessment that the subject is unlikely to receive further clinical benefit with continued treatment. For rare situations when the confirmatory scan confirms progressive disease, but the investigator believes that continued treatment is appropriate, a decision will be made jointly by the investigator and sponsor. If the patient experiences rapid clinical deterioration as perceived by the investigator before the next scheduled radiographic assessment of original PD, the investigator can discontinue study treatment without further objective evidence of disease progression and report it as progression.

9.3.14.2 Requested Prescreening Imaging and Exploratory Tumor Kinetic Modeling

To explore the relationship between response and study drug treatment, diagnostic quality prescreening CT and/or MRI scans documenting the patient's last objective response of SD or progressive disease prior to the scan at screening should be collected, as available. The RECIST v1.1 response criteria do not take into account the inherent patient-to-patient variability in tumor growth rates before treatment and therefore may not distinguish whether "SD," for example, is a reflection of treatment effect versus the natural history of an indolent tumor. A most recent prescreening CT and/or MRI scan (performed within a timeframe of no more than 3 months before the screening date for this study) will be requested for all patients in this study, if available. Collection of these scans may facilitate estimation of prestudy tumor growth rates as part of the exploratory modeling exercise intended to characterize the antitumor benefit. Prescreening images, when available, should be submitted to the imaging core laboratory vendor for potential retrospective central reading.

9.3.15 Biomarker, Pharmacodynamic, and PK Samples

9.3.15.1 Primary Specimen Collection

The primary specimen collection is presented in Table 9.d; collection of all samples listed are mandatory, with the exception of the biopsies specifically for patients within phase 2 with melanoma consistent with subgroups I and II. Biopsies are considered optional for those patients until futility has been met, at which point they will become mandatory. Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix B for plasma concentration measurements of modakafusp alfa/pembrolizumab and Appendix A for biomarker assessments.

The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible. Timing of tumor biopsy procedures can be found in Appendix A.

A sample for blood typing is to be taken only at screening. Blood banks need to be alerted that the patient is going to receive an anti-CD38 antibody that may interfere with blood typing in a manner similar to daratumumab. If the blood bank issues a compatibility card, it should be made available to the patient. The patient needs to tell other healthcare providers that he/she is receiving an anti-CD38 antibody if, for example, a blood transfusion is needed.

If necessary, plasma samples collected for PK assessments may also be used for exploration of pharmacodynamic biomarkers. These plasma PK samples may only be used for this purpose after the final PK analysis has been completed.

Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.d Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use
Fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block/slides	DNA RNA	Biomarker measurements
Blood sample for mass cytometry (immunoprofiling)	Blood	PBMC	N/A	Pharmacodynamic measurements (immunoprofiling)
Blood sample for flow cytometry (CD38 occupancy in PBMCs)	Blood	PBMC	N/A	Pharmacodynamic measurements (CD38 occupancy)
Blood sample for immunophenotyping	Blood	N/A	N/A	Pharmacodynamic measurements
Blood sample for receptor occupancy	Blood	N/A	N/A	Pharmacodynamic measurements
Serum sample for circulating biomarkers	Serum	N/A	N/A	Biomarker measurements
Blood sample for DNA	Blood	DNA	N/A	Pharmacogenetic measurements
Blood sample for RNA	Blood	RNA	N/A	Pharmacodynamic measurements
Blood sample for receptor sequencing	Blood	DNA	N/A	Pharmacodynamic measurements
Blood sample for circulating tumor cells	Blood	Cells	N/A	Biomarker Measurement
Plasma for cfDNA	Plasma	N/A	N/A	Biomarker Measurement
Serum sample for modakafusp alfa PK	Serum	N/A	N/A	PK measurements (drug concentrations)
Serum sample for Pembrolizumab PK	Serum	N/A	N/A	PK measurements (pembrolizumab concentrations)
Serum sample for immunogenicity (ADA)	Serum	N/A	N/A	Immunogenicity measurements (ADA)

ADA: antidrug antibody; cfDNA: cell-free DNA; FFPE: formalin-fixed, paraffin-embedded; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetic.

9.3.15.2 Fresh Tumor Tissue Biopsy Sample

At least 1 target lesion amenable for biopsy is required for enrollment in phase 1b. A minimum of 1 target lesion for response assessment is required for enrollment in phase 2. A separate lesion

amenable for biopsy is required for enrollment in phase 2 for cohorts I and II post futility analysis and for all patients (safety lead-in and expansion) in cohort III.

New (fresh) biopsies at screening and on-treatment will be required for all patients in phase 1b and cohort III (safety lead-in and expansion) of phase 2. For patients in cohorts I and II of phase 2, new (fresh) screening and on-treatment biopsies will be optional up until futility is met. Once futility has been met for either cohort I or II, new (fresh) biopsies will be required at screening and on-treatment.

The timing of on-treatment biopsies will be dependent on when the patient enrolls in the study. For patients enrolled in Phase 1b and those enrolled prior to futility being met within the 3 expansion cohorts of Phase 2, on-treatment biopsies will be collected on C2D2. For patients enrolled after futility has been met within any of the phase 2 expansion cohorts, on-treatment biopsies will be collected at the end of Cycle 2 to coincide with imaging assessments, prior to initiating Cycle 3.

The accessible lesion for biopsy should not have been previously irradiated or designated as the only target lesion for measurable disease (expansion phase only).

9.3.15.3 PK Measurements

Serum samples for modakafusp alfa and pembrolizumab PK will be collected at the time points specified in Appendix B.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Laboratory Manual.

The timing, but not the total number of samples, may be modified during the study on the basis of emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK of modakafusp alfa.

9.3.15.4 Biomarkers and Pharmacodynamic Measurements

In this study, several biomarkers will be assessed to test for correlation with safety and, if possible, with efficacy. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a higher probability of response or of adverse reactions to modakafusp alfa. The biomarker sample analyses will be performed if or when required. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot be anticipated.

For this purpose, blood samples will be collected as detailed in Appendix A.

9.3.15.4.1 Biomarker Measurements

Blood Sample for Circulating Tumor Cells

During dose expansion only, a whole blood sample will be collected to quantify CTCs at baseline and correlate with response to modakafusp alfa.

Plasma Sample for cfDNA

A plasma sample will be collected at baseline for evaluation of cfDNA. From the cfDNA, circulating tumor DNA will be evaluated to assess tumor mutations.

Serum Samples for Circulating Biomarkers

Serum samples will be collected to monitor circulation biomarker changes upon treatment. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a higher probability of response or of adverse reactions to modakafusp alfa. The biomarker sample analyses will be performed if or when required. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot be anticipated. In case of an infusion reaction, blood collection should be performed for central evaluation of circulating biomarkers (see Section 8.10.1).

9.3.15.4.2 Pharmacodynamic Measurements

Blood Sample for Flow Cytometry

Blood samples will be collected for flow cytometric analysis as detailed in Appendix A to determine CD38 RO and density of peripheral immune cells at baseline and at multiple time points around the first and second administrations of modakafusp alfa.

Blood Sample for Receptor Occupancy

Blood samples will be collected for flow cytometric analysis as detailed in Appendix A to determine CD38 RO and density of peripheral blood immune cells, in the presence of pembrolizumab, at baseline and at multiple time points surrounding the first and third administration of modakafusp alfa.

Blood Sample for Mass Cytometry

Blood samples will be collected for profiling of immune cells before, during, and at the end of treatment as detailed in Appendix A using mass cytometry methods. These blood samples will be analyzed for the presence and changes of immune cell populations (percentage or activation/exhaustion state), including, but not limited to B and T lymphocytes, monocytes, and NK cells.

Blood Sample for Immunophenotyping

Blood samples will be collected for assessment of immunophenotypic changes of circulating immune cells, induced by modakafusp alfa, utilizing flow cytometry techniques as detailed in Appendix A. These blood samples will be analyzed for the presence and changes of immune cell populations (percentage or activation/exhaustion state), including but not limited to B and T lymphocytes, monocytes, NK cells and dendritic cells.

Blood Sample for RNA

Blood samples for RNA will be collected at the time points specified in Appendix A for sequencing to monitor gene expression changes as a pharmacodynamic effect of modakafusp alfa administration. Sample analysis will be performed at a central laboratory.

Blood Sample for Receptor Sequencing

To monitor for induction of an adaptive immune response, blood samples will be collected to sequence T-cell and B-cell receptors. Sample analysis will be performed at a central laboratory.

9.3.16 DNA Measurements

In this study, a blood sample will be collected from each patient (unless local regulations prohibit testing) for a potential pharmacogenetic assessment as detailed in Appendix A. Pharmacogenetic assessment potentially includes the association analysis of both known and unknown DNA genetic variations to the drug activity. This sample will be analyzed in a central laboratory.

9.3.17 Immunogenicity Sample Collection

Serum samples for the assessment of antibodies to the drug product including anti–modakafusp alfa antibodies will be collected at the time points specified in Appendix A and outlined in the Laboratory Manual. Samples must be collected before study drug is administered on a dosing day, and optionally at an unscheduled visit for any patient who experiences a Grade ≥2 hypersensitivity/IRR (Section 8.1). Confirmed positive ADAs will be assayed for titer and binding domain specificity characterization. These samples will be analyzed at a central laboratory. In case of an infusion reaction, blood collection should be performed for central evaluation of immunogenicity (see Section 8.10.1).

9.4 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are discontinued from study drug and 1 or more of the following situations occur:

- Death.
- Consent withdrawal.
- Investigator decision.
- Study terminated by the sponsor.
- Lost to follow-up.
- Transfer of patient to a long-term safety study or similar program.

The consequence of consent withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

Once study has been completed, all study procedures outlined for the end of study visit will be completed as specified in the SOE (Appendix A). After study completion, no new information will be collected from the completed patient and added to the existing data or any database.

9.5 Discontinuation of Modakafusp Alfa Treatment and Patient Replacement

Treatment must be permanently discontinued if any of the criteria detailed in Section 8.6.4 are met.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in Appendix A. The primary reason for study drug discontinuation will be recorded on the eCRF.

During Cycle 1 of the dose escalation phase, patients who are discontinued prematurely for reasons other than a DLT will be replaced.

9.6 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.7 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up should occur every 12 ± 1 weeks from the EOT until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first.

After disease progression or starting another systemic anticancer therapy, all patients will be followed every 12 ± 1 weeks for OS until death or study termination. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieval from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

See Appendix A for appropriate assessments during follow-up.

NOTE: Treatment-related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, effective 01 April 2018. The signs and symptoms of disease progression should be reported as AEs in the appropriate section of the eCRF, however should not be reported by the Preferred Term (PT) of disease progression. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however,

may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Adverse Events of Special Interest (AESI)

An AESI (serious or nonserious) is an AE of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to Takeda sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's seriousness or causal relationship. Instruction regarding how and when AESIs should be reported to Takeda are provided in Section 10.2.1.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as single comprehensive event.

Regardless of causality, SAEs must be reported by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report, the preferred method of reporting SAEs. If access to EDC is not feasible within 24 hours of receiving the event, the paper SAE forms should be submitted via fax (see fax numbers below). If a fax is used for transmission, site personnel must make every effort to confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day.

E-mail submission of scanned SAE forms should only be used in the event fax transmission is not possible and EDC transmission is not feasible within 24 hours of receiving the event. If e-mail is used, site personnel must make every effort to confirm successful transmission by awaiting acknowledgment of receipt via e-mail within 1 business day.

If SAEs are reported via fax or by e-mail, the EDC system must be updated as soon as possible with the appropriate information. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC

SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

Fax Numbers

United States and Canada
+1-800-963-6290

Rest of world
+1-202-315-3560

E-Mail Address

takedaoncocases@cognizant.com

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed *before study drug was given* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, effective date 01 April 2018. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.2.1 AESI Reporting

10.2.1.1 Modakafusp Alfa

An IRR is a type of hypersensitivity reaction that develops during or shortly after administration of a drug. Signs and symptoms may include pruritus, urticaria, fever, rigors/chills, diaphoresis, bronchospasms, and cardiovascular collapse. Specific management instruction is included in Section 8.10.1. In modakafusp alfa studies, IRRs are designated as AESIs. When reporting IRRs in the eCRF, the signs and symptoms should be recorded and should be marked as an AESI.

10.2.1.2 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.

Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's causal relationship. Further, patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion.

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs. The reporting period for irAEs (Section 8.6.3.2) is extended to 90 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug, even if the patient starts nonprotocol therapy, and recorded in the eCRF. The reporting period for serious irAEs is extended to 90 days after administration of the last dose of study drug. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Any participant who is found to be pregnant during the study should be withdrawn and modakafusp alfa, and pembrolizumab if applicable, immediately discontinued. In addition, any pregnancies in the partner of a study participant during the study should also be recorded, after authorization from the study participant's partner.

If a participant or a study participant's partner agrees to their primary care physician being informed, the investigator should notify the primary care physician that the participant was participating in a clinical study at the time of the pregnancy and provide details of the study drug the subject received.

All pregnancies, including those in partners of study participants, will be followed to final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided in the Study Manual.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided in the Study Manual.

Product complaints in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, external data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will arrange to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1 Determination of Sample Size

13.1.1 Phase 1b Dose Escalation

It is expected that approximately 30 patients will be enrolled in Phase 1b. A minimum of 3 patients will be enrolled in the starting dose level. Starting from the second dose level, an adaptive BLRM guided by the EWOC principle will be used for all subsequent dose escalation recommendations. The details of the dose escalation are specified in Section 8.3 and the description and operating characteristics of the BLRM for dose escalation are included in Appendix E.

13.1.2 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 was 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]

13.2 Analysis Sets

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose (even incomplete) of modakafusp alfa.

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 response assessment.

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient data to calculate at least 1 PK parameter for modakafusp alfa.

13.3 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics including gender, age, race, weight, height, and other parameters as appropriate will be summarized using descriptive statistics. No inferential statistics will be carried out. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

13.4 Efficacy Analysis

Efficacy endpoints include ORR, DCR, DOR, PFS, and OS. No formal statistical tests will be performed for these efficacy endpoints.

ORR is defined as the proportion of patients who achieve CR or PR (determined by the investigator) during the study in response-evaluable population.

DCR is defined as the proportion of patients who achieve CR, PR, or SD (determined by the investigator) during the study in response-evaluable population.

DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders (PR or better). Responders without documentation of PD will be censored at the date of last response assessment that is SD or better.

TTP is the time from the date of the date of the first dose of study drug to the date of the first documentation of PD according to RECIST v1.1.

PFS is defined as the time from the date of the first dose of study drug to the date of first documentation of PD according to RECIST v1.1 or death due to any cause, whichever occurs first. Patients without documentation of PD or death will be censored at the date of the last response assessment that is SD or better.

OS is defined as the time from the date of first dose of study drug to the date of death due to any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

ORR and DCR will be summarized using descriptive statistics with 95% CIs. PFS and OS will be analyzed descriptively using the Kaplan-Meier method for the safety analysis set. DOR will also be analyzed using the Kaplan-Meier method for the response-evaluable analysis set.

13.5 PK Analysis

13.5.1 PK Noncompartmental Analysis

Modakafusp alfa PK parameters will be estimated using noncompartmental methods with Phoenix WinNonlin. The PK parameters will be estimated from the concentration-time profiles for the PK analysis set. The following PK parameters 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}.

Modakafusp alfa PK parameters will be summarized using descriptive statistics. Individual modakafusp alfa concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

13.5.2 PK Sampling Intended for Population PK Analysis

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. If applicable, the analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

13.6 Pharmacodynamic Analysis

During the clinical development of modakafusp alfa, several biomarkers will be assessed to test for their correlation with safety and, if possible, with efficacy. Markers that will be studied are markers linked either to the drug itself or to the treated disease. Markers of immune system activation will be summarized using descriptive statistics. Individual data will be listed. Summaries will be provided separately for each study phase and by dose, as applicable.

13.7 PK/Pharmacodynamic Analysis

Exposure-response relationships between modakafusp plasma exposure and pharmacodynamic response (eg, RO, degree of immune activation, changes in cytokines/chemokines, gene expression changes) may be explored on an ongoing basis as PK and pharmacodynamic data become available to understand the PK-pharmacodynamic relationship of modakafusp alfa and to help in estimation of the PAD. Data permitting, mathematical models may be used to describe this relationship and such models may be used to predict the dose of modakafusp alfa that provides the desired exposure and pharmacological response for future evaluation. If applicable, these data may be presented graphically as well as summarized in the clinical study report.

13.8 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 plasma concentration and effects on heart rate and QTcF interval will be analyzed using nonlinear mixed effects 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.

13.9 Immunogenicity Analyses

The proportion of patients with positive ADA (transient and persistent, titer and specificity) during the study will be summarized. The effect of immunogenicity on modakafusp alfa and pembrolizumab PK, pharmacodynamics, safety, and efficacy will be examined, if possible.

Analysis will be based on available data from patients with a baseline assessment and/or postbaseline immunogenicity assessment (safety analysis set). Summaries will be provided separately for each study phase and by dose, as applicable. These analyses will be exploratory in nature, and all results will be descriptive in nature.

13.10 Safety Analysis

The safety and tolerability of modakafusp alfa will be assessed by the recording of TEAEs (NCI CTCAE, Version 5.0), vital signs, chemistry and hematology, urinalysis, ECG, and concomitant medications.

AEs will be coded using the MedDRA. TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be summarized by MedDRA System Organ Class and PT in the safety analysis set.

13.11 [redacted]

[redacted]

[redacted]

Table 13.a [redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], and the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting

must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if

applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

When appropriate, a separate ICF will inform patients of the possibility of pseudoprogression as well as the potential risks and benefits of continuing treatment in these circumstances.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via e-mail/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial.

The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.3.1 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedules of Events

16.1 Table 16.a Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 (Phase 1b Dose Escalation)

Table 16.a Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 (Phase 1b Dose Escalation Phase)

Study Period or Treatment Cycle	Screening	Cycle 1						Cycle 2					
Day	≤21	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15
Window Allowed		0	0	0	0	±2 d	±2 d	±2 d	0	0	0	±2 d	±2 d
Informed consent [a]	X												
Eligibility criteria	X												
Demographics	X												
Medical history	X												
Prior medication and treatment history	X												
Height *(screening only)* and weight	X							X					
ECOG performance status	X	X						X					
12-lead ECG [b]	X	X						X					
Triplicate 12-lead ECG [b]		(X)	(X)										
Physical examination	X	X						X					
Vital signs [c]	X	X						X					
Monitoring of concomitant medication/procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.												
AE reporting	**SAEs** will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol systemic therapy.												
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol systemic therapy.												
Dosing													
Modakafusp alfa infusion [d]		X						X					
Disease Assessment													
CT/MRI scans [e]	X												

Table 16.a Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 (Phase 1b Dose Escalation Phase)

Study Period or Treatment Cycle	Screening	Cycle 1						Cycle 2					
Day	≤21	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15
Window Allowed		0	0	0	0	±2 d	±2 d	±2 d	0	0	0	±2 d	±2 d
Laboratory Assessments													
Chemistry [f]	X	(X)				X	X	X				X	X
Blood type [g]	X												
Hematology [h]	X	(X)				X	X	X				X	X
Blood sample for TBNK assay (*only local analysis if available*) [i]		X				X		X					
Urinalysis [j]	X												
Pregnancy test [k]	(X)	(X)						X					
Tumor biopsy [l]	X								X				
Serum sample for modakafusp alfa PK [m]	Please refer to Table 16.f below.												
Blood sample for mass cytometry (immunoprofiling) [n]		X [o]	X			X		X [o]	X			X	
Blood sample for flow cytometry (CD38 occupancy)		X [p]	X				X	X [p]	X				
Serum sample for circulating biomarkers [q]		X [p]	X			X	X	X [p]	X			X	
Serum sample for immunogenicity (ADA) [d, q]		X						X					
Blood sample for DNA [r]	X												
Blood sample for RNA		X [o]	X					X [o]	X				
Blood sample for receptor sequencing		X [o]				X		X [o]					
Plasma for cfDNA		X [o]											

Footnotes on last page.

16.2 Table 16.b Schedule of Events, Continued: Cycle 3 Through Cycle 6 (Phase 1b Dose Escalation)

Table 16.b Schedule of Events, Continued: Cycle 3 Through Cycle 6 (Phase 1b Dose Escalation)

Treatment Cycles	Treatment Cycle 3 Through Cycle 6				
Cycle	Cycle 3	Cycle 4		Cycle 5	Cycle 6
Day	Day 1	Day 1	Day 2	Day 1	Day 1
Window Allowed	±2 d	±2 d	0 d	±2 d	±2 d
Weight	X	X		X	X
ECOG performance status	X	X		X	X
Directed physical examination	X	X		X	X
Vital signs [c]	X	X		X	X
Monitoring of concomitant medication and procedures					
AE reporting					
Dosing					
Modakafusp alfa infusion [d]	X	X		X	X
Disease Assessment					
CT/MRI scans [e]	Repeat every 6 weeks through Cycle 6 then every 9 weeks thereafter.				
Laboratory Assessments					
Chemistry [f]	X	X		X	X
Hematology [h]	X	X		X	X
Blood sample for TBNK assay (*only local analysis if available*) [i]	X				
Pregnancy test [k]	X	X		X	X
Serum sample for modakafusp alfa PK [m]	Please refer to Table 16.f below.				
Blood sample for mass cytometry (immunoprofiling) [n]		X [o]	X		
Serum sample for circulating biomarkers [d]		X [p]	X		
Serum sample for immunogenicity (ADA) [d, q]	X	X		X	X
Blood sample for RNA		X [o]	X		
Blood sample for receptor sequencing		X [o]			

16.3 Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation)

Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation)

Study Period or Treatment Cycle	Cycles 7, 10, 13, and 16+	Cycles 8, 11, 12, and 14	Cycle 9 and Cycle 15		EOT	Follow-up	
						PFS [s]	OS [t]
Day	Day 1	Day 1	Day 1	Day 2	30 (+10) Days After Last Dose or Before Start of Subsequent Systemic Anticancer Therapy, Whichever Occurs First	Q12W	
Window Allowed	±4 d	±4 d	±4 d	0		±1 week	
Weight	X	X	X				
ECOG performance status	X	X	X				
12-lead ECG [b]					X		
Directed physical examination	X	X	X				
Vital signs [c]	X	X	X				
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.						
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.						
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol systemic therapy.					Only study drug-related SAEs will be reported.	
Dosing							
Modakafusp alfa infusion [d]	X	X	X				
Disease Assessment							
CT/MRI scans [e]	Repeat every 6 weeks through Cycle 6 then every 9 weeks thereafter.					X	

Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation)

Study Period or Treatment Cycle	Cycles 7, 10, 13, and 16+	Cycles 8, 11, 12, and 14	Cycle 9 and Cycle 15		EOT	Follow-up	
						PFS [s]	OS [t]
Day	Day 1	Day 1	Day 1	Day 2	30 (+10) Days After Last Dose or Before Start of Subsequent Systemic Anticancer Therapy, Whichever Occurs First	Q12W	
Window Allowed	±4 d	±4 d	±4 d	0		±1 week	
Laboratory Assessments							
Chemistry [f]	X	X	X				
Hematology [h]	X	X	X				
Pregnancy test [k]	X	X	X		X		
Serum sample for modakafusp alfa PK [m]	Please refer to Table 16.f below.						
Blood sample for mass cytometry (immunoprofiling) [n]			X [o]	X	X		
Serum sample for circulating biomarkers [d]			X [p]	X	X		
Serum sample for immunogenicity (ADA) [d, q]	X	X	X		X		
Blood sample for RNA			X [o]	X	X		
Blood sample for receptor sequencing			X [o]				
OS Follow-up							
Survival							X
Subsequent therapy						X	

ADA: antidrug antibody; AE: adverse event; CxDx: Cycle x Day x; cfDNA, cell-free DNA; CT: computed tomography; d: day(s); ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; ICF: informed consent form; IRR: infusion-related reaction; RECIST: Response Evaluation Criteria in Solid Tumors; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic(s); Q3W: once every 3 weeks; Q12W: once every 12 weeks; QTc: corrected QT interval; RBC: red blood cell; SAE: serious adverse event; SOE: Schedule of Events; TBNK: quantification of T cells (including CD4+ and CD8+ T cells), B cells, and natural killer cells; TSH: thyroid stimulating hormone; WBC: white blood cell.
Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

[a] Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window. The screening period is 21 days and runs between ICF signature and first dose unless it is explicitly

specified otherwise.

[b] For all participant patients in the trial, QTc duration should be assessed locally with 1 standard local ECG to be collected and read at screening, at predose of C1D1 and C2D1, and at EOT. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. Triplicate ECGs will be obtained as described in these SOEs and in Table 16.f. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation.

[c] Vital signs will be measured before starting the infusion and after the completion of the infusion. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Blood pressure will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any moment if the patient complains of symptoms consistent with an IRR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient cannot be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour. During the infusion and for 6 hours postinfusion in the first 2 treatment cycles, patients should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage IRRs. In Cycle 3 and beyond, patients should be continually monitored for at least 2 hours after the end of infusion, and the monitoring duration can be extended per a patient's prior dosing experience.

[d] In case of an infusion reaction of Grade ≥2, blood draws should be performed for central evaluation of immune markers, cytokines, chemokines, and ADAs. The following samples should be collected: serum sample for circulating biomarkers, and serum sample for immunogenicity.

[e] CT and/or MRI scans will be performed at screening unless chest, abdominal cavity, and pelvis diagnostic quality scans were performed within 5 weeks before the planned first dose of study drug. CT and/or MRI scans of the chest, abdominal cavity, and pelvis should be acquired with at least IV contrast. The imaging modalities used for a patient should remain consistent throughout the study. If contrast-enhanced CT scans are contraindicated for a particular patient, a noncontrast-enhanced CT of the chest should be acquired if possible, in addition to contrast-enhanced CT of the abdomen, and pelvic MRI. Repeat CT and/or MRI scans should be performed every other cycle up to Cycle 7 (Day 1 [-7 days] of Cycles 3, 5, and 7), every 3 cycles thereafter, and as clinically indicated. Response will be determined locally according to RECIST v1.1 (see Section 9.3.14.1). Screening and on-treatment images, when available, should be transferred to the imaging core laboratory vendor for potential retrospective central reading. Clinical decisions will be made per local response assessment. Availability of prescreening scan(s) is not a prerequisite for study eligibility (Section 9.3.14.2). If available, the most recent prescreening diagnostic quality CT and/or MRI scans dated within 3 months before the planned first dose of modakafusp alfa should be submitted to the imaging core laboratory vendor for potential retrospective central reading. The date of the scan should be indicated. Response assessment will be calendar-based regardless of treatment delays/interruptions.

[f] Chemistry will include tests listed in Table 9.a. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 4 days old.

[g] A sample for blood typing to be taken only at screening. Blood banks need to be alerted that the patient is going to receive an anti-CD38 antibody that may interfere with blood typing in a manner similar to daratumumab. If the blood bank issues a compatibility card, it should be made available to the patient. The patient needs to tell other healthcare providers that he/she is receiving an anti-CD38 antibody if, for example, a blood transfusion is needed.

[h] Hematology will include tests listed in Table 9.a. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 4 days old.

[i] Blood samples for TBNK (T cells [including CD4+ and CD8+ T cells], B cells, and NK cells) flow cytometric analysis will be obtained predose on indicated visits, only if local analysis is available at the site.

[j] Urinalysis (dipstick) will include tests listed in Table 9.a. Microscopic if clinically indicated only: bacteria, RBCs, WBCs, casts, and crystals.

[k] A serum or urine pregnancy test will be performed for patients of childbearing potential with negative results during screening and again at C1D1 (baseline) if the screening test was performed more than 72 hours before the C1D1 dosing. A serum or urine pregnancy test must be performed at predose (within 72 hours prior to dosing) on Day 1 of each cycle with negative results available before modakafusp alfa is administered. A serum or urine pregnancy test is required at EOT.

[l] At least 1 target lesion amenable for biopsy is required for enrollment in phase 1b. The accessible biopsy lesion should not have been previously irradiated. See Section 9.3.15.2 for details.

[m] Blood samples for modakafusp alfa PK will be collected at timepoints specified in Table 16.f below.

[n] Immunoprofiling consists of mass cytometric analysis of T, B, and NK lymphocyte subsets, and will be analyzed centrally.

[o] Predose.

[p] Predose and at 4 hours (+/- 30 minutes) after the end of infusion.

[q] Blood samples for immunogenicity (ADA) testing will be collected before the dose on Day 1 of every cycle while the patient remains in treatment and, if possible, at the EOT follow-up visit. In case of an infusion reaction, blood draws should be performed for central evaluation of immunogenicity.

[r] One blood sample for DNA will be taken at either screening or C1D1 predose (when it is not possible to collect at screening, samples can be collected at the next visit).

[s] Patients who discontinue modakafusp alfa for reasons other than PD will continue PFS follow-up every 12±1 weeks from the EOT visit until the occurrence of PD, death, the start of subsequent systemic anticancer therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. PFS will be assessed according to RECIST v1.1 (Section 9.3.14.1).

[t] Patients will be followed for survival every 12±1 weeks until death, loss to follow-up, consent withdrawal, or study termination. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieval from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

16.4 Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion)

Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion)

Study Period or Treatment Cycle	Screening	Cycle 1						Cycle 2		Cycle 3					
Day	**≤21**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 2**	**Day 1**	**Day 2**	**Day 3**	**Day4**	**Day 8**	**Day 15**
Window Allowed		**0**	**0**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**0**	**±2 d**	**±0 d**	**0**	**0**	**±2 d**	**±2 d**
Informed consent [a]	X														
Eligibility criteria	X														
Demographics	X														
Medical history	X														
Prior medication and treatment history	X														
Height *(screening only)* and weight	X							X		X					
ECOG performance status	X	X						X		X					
12-lead ECG [b]	X	X						X		X					
Triplicate 12-lead ECG [b]		(X)	(X)												
Physical examination	X	X						X		X					
Vital signs [c]	X	X						X		X					
Monitoring of concomitant medication/procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.														
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first. The reporting period for irAEs is extended to 90 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.														
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol systemic therapy. Serious irAEs will be reported through 90 days after last dose of study drug.														
Dosing															
Modakafusp alfa infusion [d]		X						X		X					
Pembrolizumab infusion [e]		X								X					
Disease Assessment															
CT/MRI scans [f]	X	Repeat every 6 weeks through Cycle 6 then every 9 weeks thereafter.													

Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion)

Study Period or Treatment Cycle	Screening	Cycle 1						Cycle 2		Cycle 3					
Day	≤21	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15	Day 1	Day 2	Day 1	Day 2	Day 3	Day4	Day 8	Day 15
Window Allowed		0	0	0	0	±2 d	±2 d	±2 d	0	±2 d	±0 d	0	0	±2 d	±2 d
Laboratory Assessments															
Chemistry [g]	X	(X)				X	X	X		X				X	X
Blood type [v]	X														
Hematology [h]	X	(X)				X	X	X		X				X	X
Urinalysis [j]	X	X						X		X					
Pregnancy test [k]	(X)	(X)						(X)		(X)					
Immunosafety markers [l]	X									X					
Tumor biopsy [m]	(X)								(X) [x]	(X) [y]					
Serum sample for modakafusp alfa PK [n]	Please refer to Table 16.g and Table 16.h below.														
Pembrolizumab PK [n]	Please refer to Table 16.g and Table 16.h below.														
Blood sample for immunophenotyping [o]		X [p]	X	X		X		X [p]	(X) [x]	X [p]	X	X		X	
Blood sample for receptor occupancy		X [q]	X	X		X				X [q]	X	X			
Serum sample for circulating biomarkers [d]		X [q]	X	X		X		X [q]	(X) [x]	X [q]	X	X		X	
Serum sample for immunogenicity (ADA) [d, r]		X						X		X					
Blood sample for DNA [s]	X														
Blood sample for RNA		X [p]	X	X				X [p]	(X) [x]	X [p]	X	X			
Blood sample for receptor sequencing		X [p]				X		X [p]		X [p]					
Blood sample for circulating tumor cells [w]		X [p]													
Plasma for cfDNA		X [p]													

Footnotes are on the last page of the SOE.

16.5 Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)

Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)

Study Period or Treatment Cycle	**Cycles 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, and 16+**	**Cycle 7 and Cycle 15**		**EOT**	**Follow-up**	
					PFS [t]	**OS [u]**
Day	**Day 1**	**Day 1**	**Day 2**	**30 (+10) Days After Last Dose or Before Start of Subsequent Systemic Anticancer Therapy, Whichever Occurs First**	**Q12W**	
Window Allowed	**±4 d**	**±4 d**	**0**		**±1 week**	
Weight	X	X				
ECOG performance status	X	X				
12-lead ECG [b]				X		
Directed physical examination	X	X				
Vital signs [c]	X	X				
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first. The reporting period for irAEs is extended to 90 days after administration of the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.					
AE reporting	Recorded from signing of the ICF through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.					
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug even if the patient starts nonprotocol systemic therapy. Serious irAEs will be reported through 90 days after last dose of study drug.				Only study drug-related SAEs will be reported.	
Dosing						
Modakafusp alfa infusion [d]	X	X				
Pembrolizumab infusion [e]	(X)	X				
Disease Assessment						
CT/MRI scans [f]	Repeat every 6 weeks through Cycle 6 then every 9 weeks thereafter.				X	

Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)

Study Period or Treatment Cycle	Cycles 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, and 16+	Cycle 7 and Cycle 15		EOT	Follow-up	
					PFS [t]	OS [u]
Day	Day 1	Day 1	Day 2	30 (+10) Days After Last Dose or Before Start of Subsequent Systemic Anticancer Therapy, Whichever Occurs First	Q12W	
Window Allowed	±4 d	±4 d	0		±1 week	
Laboratory Assessments						
Chemistry [g]	X	X				
Hematology [h]	X	X				
Urinalysis [j]	X	X		X		
Pregnancy test [k]	(X)	(X)		(X)		
Immunosafety markers [l]	(X)	X		X		
Serum sample for modakafusp alfa PK [n]	Please refer to Table 16.g and Table 16.h below.					
Serum sample for pembrolizumab PK [n]	Please refer to Table 16.g and Table 16.h below.					
Blood sample for immunophenotyping [o]		X [p]	X	X		
Serum sample for circulating biomarkers [d]		X [q]	X	X		
Serum sample for immunogenicity (ADA) [d, r]	X	X		X		
Blood sample for RNA		X [p]	X	X		
Blood sample for receptor sequencing		X [p]				
OS Follow-up						
Survival						X
Subsequent therapy					X	

ADA: antidrug antibody; AE: adverse event; CxDx: Cycle x Day x; cfDNA, cell-free DNA; CT: computed tomography; CTCs: circulating tumor cells; d: day(s); ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; ICF: informed consent form; IRR: infusion-related; RECIST: Response Evaluation Criteria in Solid Tumors; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic(s); Q3W: once every 3 weeks; Q12W: once every 12 weeks; QTc: corrected QT interval; RBC: red blood cell; SAE: serious adverse event; SOE: Schedule of Events; TBNK: quantification of T cells (including CD4+ and CD8+ T cells), B cells, and natural killer cells; TSH: thyroid-stimulating hormone;

WBC: white blood cell.
Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

[a] Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window. The screening period is 21 days and runs between ICF signature and first dose unless it is explicitly specified otherwise.

[b] For all participant patients in the trial, QTc duration should be assessed locally with 1 standard local ECG to be collected and read at screening, at predose and at the end of modakafusp alfa infusion (+ 30 minute window) of C1D1, C2D1 and C3D1, and at EOT. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. During the safety lead-in dose expansion phase, triplicate ECGs will be obtained as described in these SOEs and in Table 16.g. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation.

[c] Vital signs will be measured before starting the infusion and after the completion of the infusion. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. Blood pressure will be measured every 30 minutes (±5 minutes) during the first 4 infusions, after the end of the infusion, and at any moment if the patient complains of symptoms consistent with an IRR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient cannot be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour. During the first infusion and for 6 hours postinfusion in the first 2 treatment cycles, patients should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage IRRs. In Cycle 3 and beyond, patients should be continually monitored for at least 2 hours before the end of infusion, and the monitoring duration could be extended per a patient's prior dosing experience.

[d] In case of an IRR, blood draws should be performed for central evaluation of cytokines, chemokines, complement, immune complex formation and ADAs. The following samples should be collected: serum sample for circulating biomarkers and serum sample for immunogenicity.

[e] The recommended pembrolizumab dose of 400 mg will be administered as an IV infusion over 30 ±10 minutes Q6W. Pembrolizumab will be administered before modakafusp alfa on days when both modakafusp alfa and pembrolizumab are given. At least 30 minutes should elapse between the completion of the infusion of the pembrolizumab and the infusion of modakafusp alfa.

[f] CT and/or MRI scans of the chest, abdominal cavity, and pelvis should be acquired with at least IV contrast. The imaging modalities used for a patient should remain consistent throughout the study. If IV contrast-enhanced CT scans are contraindicated for a particular patient, a noncontrast-enhanced CT of the chest should be acquired in addition to an oral contrast–enhanced CT of the abdomen and IV contrast–enhanced pelvic MRI. At present, low-dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Repeat CT and/or MRI scans should be performed every other cycle up to Cycle 7 (Day 1 [-7 days] of Cycles 3, 5, and 7), every 3 cycles thereafter, and as clinically indicated. Response will be determined locally according to RECIST v1.1 (see Section 9.3.14.1). Screening and on-treatment images, when available, should be submitted to the imaging core laboratory vendor for retrospective central reading when it is required. Clinical decisions will be made per local response assessment. Availability of prescreening scan(s) is not a prerequisite for study eligibility (Section 9.3.14.2). If available, the most recent prescreening diagnostic quality CT and/or MRI scans dated within 3 months before the planned first dose of modakafusp alfa should be submitted to the imaging core laboratory vendor for tumor growth rate determination. The date of the scan should be indicated. Response assessment will be calendar-based regardless of treatment delays/interruptions.

[g] Chemistry will include tests listed in Table 9.a. Chemistry on C1D15 and C3D15 could be assessed in a local hospital if there is no planned PK sampling on those visits per Table 16.g and Table 16.h.

[h] Hematology will include tests listed in Table 9.a. Hematology on C1D15 and C3D15 could be assessed in local hospital when there is no planned PK sampling on those visits per Table 16.g and Table 16.h.

[i] *Footnote no longer applicable.*

[j] Urinalysis (dipstick) will include tests listed in Table 9.a. Microscopic if clinically indicated only: bacteria, RBCs, WBCs, casts, and crystals.

[k] A serum or urine pregnancy test will be performed for patients of childbearing potential with negative results during screening and again at C1D1 (baseline) if the screening test was performed more than 72 hours before the C1D1 dosing. A serum or urine pregnancy test must be performed at predose (within 72 hours prior to dosing) on Day 1 of each cycle with negative results available before modakafusp alfa is administered. A serum or urine pregnancy test is required at EOT.

[l] Immunosafety lab tests include thyroid-stimulating hormone (TSH), free thyroxine (free T4) and cortisol (morning preferred) repeated every other cycle starting from Cycle 3, and at the EOT as detailed in Section 9.3.13.3. These tests are analyzed locally.

[m] A minimum of 1 target lesion for response assessment is required for enrollment in phase 2. A separate lesion amenable for biopsy is required for enrollment in cohort I and II (post futility analysis) and cohort III (all patients, inclusive of safety-lead in) of phase 2. New (fresh) biopsies at screening and on treatment will be required for all patients in cohort III (safety-lead in and expansion) of phase 2. For patients in cohorts I and II of phase 2, new (fresh) screening and on-treatment biopsies will be optional up until futility has been met. Once futility has been met for either cohorts I or II, new (fresh) biopsies will be required at screening and on-treatment. See Section 9.3.15.2 for details. The accessible lesion for biopsy should not have been previously irradiated or designated as the only target lesion for measurable disease.

[n] Blood samples for modakafusp alfa PK and pembrolizumab PK will be collected at time points specified in Table 16.g and Table 16.h below.

[o] Flow cytometry methodologies will be used to immunophenotype T, B, and NK lymphocyte subsets, and will be analyzed centrally.

[p] Predose.

[q] Predose and at 4 hours (+/- 30 minutes) after the end of infusion.

[r] Blood samples for immunogenicity (ADA) testing will be collected before the dose on Day 1 of every cycle while the patient remains in treatment and, if possible, at the EOT follow-up visit. In case of an IRR, blood draws should be performed for central evaluation of immunogenicity.

[s] One blood sample for DNA will be taken at either screening or C1D1 predose (when it is not possible to collect at screening, samples can be collected at the next visit).

[t] Patients who discontinue modakafusp alfa for reasons other than PD will continue PFS follow-up every 12±1 weeks from the EOT visit until the occurrence of PD, death, the start of subsequent systemic anticancer therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. PFS will be assessed according to RECIST v1.1.

[u] Patients will be followed for survival every 12±1 weeks until death, loss to follow-up, consent withdrawal, or study termination. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieval from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

[v] A sample for blood typing to be taken only at screening. Blood banks need to be alerted that the patient is going to receive an anti-CD38 antibody that may interfere with blood typing in a manner similar to daratumumab. If the blood bank issues a compatibility card, it should be made available to the patient. The patient needs to tell other healthcare providers that he/she is receiving an anti-CD38 antibody if, for example, a blood transfusion is needed.

[w] A whole blood sample will be collected to quantify CTCs at baseline and correlate with response.

[x] Pharmacodynamic samples to be collected for patients enrolled within the safety lead-in and those enrolled within the expansion cohorts prior to futility being met.

[y] After futility has been met within an expansion cohort, the on-treatment biopsy sample should be taken prior to Cycle 3 administration of modakafusp alfa and pembrolizumab. For convenience, biopsy can be taken up to a 7 days prior to C3D1, preferably to coincide with imaging assessments of disease.

Appendix B PK Sampling Tables

16.6 Table 16.f Serial PK (Serum) Sample Breakdown: Phase 1b Dose Escalation

Table 16.f Serial PK (Serum) Sample Breakdown: Phase 1b Dose Escalation

	Cycle 1						Cycle 2				Cycles 3-6
	C1D1		C1D2 [a]		C1D3 [a]	C1D4	C2D1 [a]	C2D2 [a]	C2D3 [a]	C2D4 [a]	D1
	Triplicate ECG [b]	PK	Triplicate ECG [b]	PK	PK	PK	PK	PK	PK	PK	PK
Predose (within 30 min before start of infusion)	X3	X1					X1				X
End of infusion (±10 min)	X3	X1					X1				X
1 h after end of infusion (±15 min)	X3	X1					X1				
2 h after end of infusion (±30 min)	X3	X1					X1				X [c]
6 h after end of infusion (±30 min)	X3	X1					X1				
24 h after end of infusion (±1 h)			X3	X1				X1			
48 h after end of infusion (±2 h)					X1				X1		
72 h after end of infusion (±2 h)						X1 [d]				X1 [d]	

CxDx: Cycle x Day x; D: Day; ECG: electrocardiogram; h: hour(s); min: minute(s); PK: pharmacokinetic(s).

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.

[a] Timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle. The date/time of the start and end of infusions should be recorded accurately. PK samples should only be collected from the contralateral arm and not from the drug infusion arm.

[b] Triplicate ECGs are collected before PK sample collection. See also Section 9.3.12. Triplicate 12-lead ECG measurements are performed using an ECG recorder. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occurs within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. The ECG data collected on these ECG recorders can also be used as safety ECGs for assessment on site by investigator (ERT will ensure ECG recorders can transmit ECGs for on-site assessment for investigator). On C1D1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours before collection of the predose ECGs until after collection of the 1 hour after end of modakafusp alfa infusion triplicate ECGs. A low-calorie and low-sodium light meal is permitted immediately after the 1-hour postinfusion ECG has been collected. Light meals are permissible immediately after collection of the 2-hour and 6-hour postinfusion ECG timepoints. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.

[c] Cycle 4 only for dose escalation phase.

[d] Only patients receiving modakafusp alfa 0.75 mg/kg or higher.

16.7 Table 16.g Serial PK (Serum) Sample Breakdown: Safety Lead-in Phase of Phase 2 Dose Expansion

Table 16.g Serial PK (Serum) Sample Breakdown: Safety Lead-in Phase of Phase 2 Dose Expansion

	Cycle 1							Cycle 3					Cycle 2, Cycle 4-beyond	
	D1[a]			D2 [a]		D3 [a]	D4	D1 [a]		D2 [a]	D3 [a]	D4 [a]	D1	
	Triplicate ECG [b]	Modak-afusp alfa PK	Pembro-lizumab PK	Triplicate ECG [b]	Modaka-fusp alfa PK	Modaka-fusp alfa PK	Modaka-fusp alfa PK	Modak-afusp alfa PK	Pembro-lizumab PK	Modaka-afusp alfa PK	Modaka-fusp alfa PK	Modaka-fusp alfa PK	Modaka-fusp alfa PK	Pembro-lizumab PKe
Predose (within 30 min before start of infusion)	X3	X1	X					X1	X				X	X
End of infusion (±10 min)	X3	X1	X					X1	X				X	X
1 h after end of infusion (±15 min)	X3	X1						X1						
2 h after end of infusion (±30 min)	X3	X1						X1					X [c]	X[c]
6 h after end of infusion (±30 min)	X3	X1	X					X1	X					
24 h after end of infusion (±1 h)				X3	X1					X1			X [d]	
48 h after end of infusion (±2 h)						X1					X1			
72 h after end of infusion (±2 h)							X1					X1		

CxDx: Cycle x Day x; D: Day; ECG: electrocardiogram; h: hour(s); min: minute(s); PK: pharmacokinetic(s).

When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.

[a] Timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle. The date/time of the start and end of infusions should be recorded accurately. PK samples should only be collected from the contralateral arm and not from the drug infusion arm.

[b] Triplicate ECGs are collected before PK sample collection. See also Section 9.3.12. Triplicate 12-lead ECG measurements are performed using an ECG recorder. Collection of triplicate ECG begins after patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs occurs within 3 minutes of each other and over a 10-minute window. When the timing of triplicate and single (safety) ECGs coincide, the site can use the triplicate ECG collection for safety evaluation. The ECG data collected on these ECG recorders can also be used as safety ECGs for assessment on site by investigator (ERT will ensure ECG recorders can transmit ECGs for on-site assessment for investigator). On C1D1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours before collection of the predose ECGs until after collection of the 1 hour after end of modakafusp alfa infusion triplicate ECGs. A low-calorie and low-sodium light meal is permitted immediately after the 1-hour postinfusion ECG has been collected. Light meals are permissible immediately after collection of the 2-hour and 6-hour postinfusion ECG timepoints. In patients unable to comply with these recommendations, any food intake should be limited to the smallest required portion of bland food.

[c] Cycle 5 only.

[d] Cycle 2 only.

[e] Blood samples for pembrolizumab PK will only be collected at the visits with pembrolizumab dosing (ie, Cycle 1, Cycle 3, Cycle 5, Cycle 7 and beyond).

16.8 Table 16.h Sparse Serum PK Sampling Schedule to Characterize PK of Modakafusp Alfa and Pembrolizumab During Phase 2 Expansion Phase (excluding Safety Lead-In Periods)

Table 16.h Sparse Serum PK Sampling Schedule to Characterize PK of Modakafusp Alfa and Pembrolizumab During Phase 2 Expansion Phase (excluding Safety Lead-In Periods)

	Cycles 1 and Beyond Day 1	
	Modakafusp Alfa PK [a]	**Pembrolizumab PK [c]**
Predose (within 30 min before start of infusion)	X1	X
End of modakafusp alfa infusion (±10 minutes)	X1	X
2-4 hours after end of modakafusp alfa infusion	X1 [b]	X [b]
Total Timepoints	**3**	

PK: pharmacokinetic(s).

[a] The timing of the morning visits should occur at approximately the same time as previous dosing days. The date/time of the start and end of infusions should be recorded accurately. PK samples should only be collected from the contralateral arm and not from the drug infusion arm.

[b] Cycles 1, 3, and 5 only.

[C] Blood samples for pembrolizumab PK will only be collected at the visits with pembrolizumab dosing (ie, Cycle 1, Cycle 3, Cycle 5, Cycle 7 and beyond).

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

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

An adaptive BLRM with overdose control principle (Babb et al. 1998; Neuenschwander et al. 2008) 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. (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-dosing.
- [0.16, 0.33]: target toxicity.
- [0.33, 1.00]: excessive toxicity.

The next recommended dose will be selected as described in Section 8.3.

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.

16.9 Appendix F Protocol History

Date	Amendment Number	Region
28 July 2022	6	Global
16 November 2021	5	Global
11 August 2021	4	Global
08 March 2021	3	Global
12 March 2020	2	Global
22 October 2019	1	Global
05 August 2019	Initial Protocol	Global

16.9.1 Protocol Amendment 5

This section describes the changes in the protocol incorporating Amendment 5. The primary reasons for this amendment are to:

- Inform all participating sites that the timeframe for contraception and egg donation has been increased to 6 months after study drug administration (modakafusp alfa or pembrolizumab) for female patients of childbearing potential enrolled in the study.
- Add urinalysis to required tests at the screening visit, Day 1 of all cycles, and the end-of-treatment (EOT) visit.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 5			
Summary of Changes since the Last Approved Protocol			
Change	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
Number	***Location***	***Description***	***Rationale***
1.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria Section 8.9 Precautions and Restrictions	The timeframe for contraception and egg donation has been amended for female patients of childbearing potential enrolled in the study.	Update.
2.	2.0 Study Summary Section 8.9 Precautions and Restrictions	Restrictions for breastfeeding were added.	Update.
3.	2.0 Study Summary Section 7.1 Inclusion Criteria Section 8.9 Precautions and Restrictions	The definition of postmenopausal was clarified for consistency.	Clarification.
4.	Section 16.4 Table 16.3	Added urinalysis to the screening visit and Day 1 of Cycles 2 and 3.	Update.
5.	Section 16.5 Table 16.e	Added urinalysis to Day 1 of all cycles and the EOT visit.	Update.

16.9.2 Protocol Amendment 4 Summary of Changes

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reasons for this amendment are to:

- Update the drug name from TAK-573 to modakafusp alfa.
- Revise endpoints and clarify text regarding samples for receptor occupancy and immunophenotyping.
- Change statement regarding sourcing of pembrolizumab.
- Correct modakafusp alfa "injection" to "infusion."
- Revise target response rates and stopping boundaries.
- Modify criteria for permitted radiotherapy on treatment.
- Add pembrolizumab time frame to contraception guidelines.
- Add description of modakafusp alfa formulations.
- Revise description of required biopsies.
- Clarify timing of T lymphocyte, B lymphocyte, and natural killer cells (TBNK) blood sampling.
- Clarify response assessment guidelines and added text regarding disposition of imaging.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4			
Summary of Changes since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Title page.	Protocol title corrected.	Correction.
2.	Throughout protocol.	Changed TAK-573 to modakafusp alfa.	Update.
3.	Section 8.15.1 Modakafusp Alfa	Revised modakafusp alfa storage, thawing, and reconstitution guidelines.	Update.
4.	2.0 Study Summary Section 5.1 Objectives Section 5.2 Endpoints Section 5.1.3 Exploratory/Additional Objectives Table 6.a Primary and Secondary Endpoints for Disclosure	Downgraded the CD38 receptor occupancy objective and endpoint from secondary to exploratory.	Update.

Protocol Amendment 4			
Summary of Changes since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	Section 2.0 Study Summary Section 5.1 Objectives Section 5.2 Endpoints Table 6.a Primary and Secondary Endpoints for Disclosure	Downgraded the Type I interferon gene expression signatures objective and endpoint to exploratory.	Update.
6.	Section 2.0 Study Summary Section 6.1.1 Phase 1b Single-Agent Dose Escalation	Added further explanation of Phase 1b dose escalation process.	Clarification.
7.	Section 8.13.2 Pembrolizumab	Changed statement regarding sourcing of pembrolizumab.	Update.
8.	Section 8.1 Study Drug Administration Section 8.12 Description of Investigational Agents	Corrected “injection” to “infusion.”	Correction.
9.	Section 8.1 Study Drug Administration	Added reference to premedication guidelines.	Clarification.
10.	8.7 Excluded Concomitant Medications and Procedures	Modified criteria for permitted radiotherapy on treatment.	Update.
11.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria Section 8.9 Precautions and Restrictions	Added pembrolizumab time frame to contraception guidelines.	Update.
12.	10.2.1.2 Pembrolizumab	Added 2 adverse events of special interest.	Update
13.	Section 8.12 Description of Investigational Agents	Added description of modakafusp alfa formulations.	Update.
14.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria Section 9.3.15 Biomarker, Pharmacodynamic, and PK Samples Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Revised description of required biopsies.	Update.
15.	Section 9.3.13.2 TBNK	Clarified timing of T lymphocyte, B lymphocyte, and natural killer cells (TBNK) blood sampling.	Clarification.

Protocol Amendment 4			
Summary of Changes since the Last Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16.	Section 9.3.14 Disease Assessment Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation) Section 9.3.3 Medical History Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Clarified response assessment guidelines and added text regarding disposition of imaging.	Update.
17.	Table 9.d Primary Specimen Collection	Added rows for immunophenotyping and receptor occupancy samples.	Clarification.
18.	Section 9.3.15.4.2 Pharmacodynamic Measurements	Added text regarding samples for receptor occupancy and immunophenotyping.	Clarification.
19.	Section 13.1 Determination of Sample Size Section 13.11 [redacted]	[redacted]	Update.
20.	Table 16.c Schedule of Events, Continued: Cycle 7 Through EOT and Follow-up (Phase 1 Dose Escalation) Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Added text regarding monitoring of patients for infusion-related reactions.	Update.
21.	Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion)	Deleted blood sample for TBNK.	Update.
22.	Table 16.d Schedule of Events: Screening, Baseline, Cycle 1, Cycle 2, and Cycle 3 (Phase 2 Dose Expansion) Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Updated terms for immunophenotyping and receptor occupancy samples.	Update.
23.	Table 16.e Schedule of Events, Continued: Cycle 4 Through EOT and Follow-up (Phase 2 Dose Expansion)	Added electrocardiogram collection at the end of modakafusp alfa infusion.	Update.
24.	Table 16.g Serial PK (Serum) Sample Breakdown: Safety Lead-in Phase of Phase 2 Dose Expansion	Removed unneeded footnotes.	Correction.

16.9.3 Protocol Amendment 03 Summary of Changes

Amendment 03 added COVID-related changes to maintain patient safety, confidentiality, and study integrity in the context of healthcare challenges presented by the coronavirus disease 2019

(COVID-19) public health emergency. The study design was changed to a phase 1b/2 study, and the disease types eligible for enrollment were revised. Study objectives and endpoints, statistical methods, and study size estimations were also revised to reflect study design changes. Other changes to the study design are described below. In addition, minor grammatical and typographical corrections were made.

Summary of Changes since the Last Approved Protocol			
Number	**Section(s) Affected by Change**	**Description**	**Rationale**
1.	Title page. Section 2.0 Study Summary Section 3.4 Corporate Identification	Update to legal entity.	Update.
2.	Section 2.0 Study Summary Section 6.3.4 Total Study Duration Table 6.a Primary and Secondary Endpoints for Disclosure	Increased estimated study completion time to 55 months.	Update.
3.	Section 2.0 Study Summary Section 4.4.3 Rationale for TAK-573 Phase 2 Expansion Phase Cohorts Section 5.0 Study Objectives and Endpoints Section 6.0 Study Design Section 7.0 Study Population Section 8.4 Phase 2 TAK-573 Dose Expansion Appendix A Schedules of Events	Added a phase 2 (dose expansion) combination treatment phase (TAK-573 + pembrolizumab 400 mg every 6 weeks) to the study which begins with enrollment of at least 3 patients in a safety lead-in.	Update.
4.	Section 2.0 Study Summary Section 7.0 Study Population Section 9.3.15.2 Fresh Tumor Tissue Biopsy Sample Appendix A Schedules of Events	Revised tumor biopsy requirements to include second sample on or after Cycle 2 and required that the lesion was not previously irradiated or designated as the only target lesion for measurable disease (phase 2 expansion only).	Update.
5.	Section 2.0 Study Summary Section 7.0 Study Population	Revised eligibility criteria to reflect changes in study design and disease cohorts permitted to enroll in phase 2.	Update.
6.	Section 2.0 Study Summary Section 5.1.1 Primary Objective Appendix A Schedules of Events	Revised primary objective to reflect addition of phase 2 treatment and disease types as detailed above.	Update.
7.	Section 2.0 Study Summary Section 5.1.2 Secondary Objectives Appendix A Schedules of Events	Revised secondary objectives to reflect addition of phase 2 treatment and disease types as detailed above and added assessment of safety/tolerability of both TAK-573 single agent (SA) and in combination with pembrolizumab.	Update.

Summary of Changes since the Last Approved Protocol			
Number	**Section(s) Affected by Change**	**Description**	**Rationale**
8.	Section 5.1.3 Exploratory/Additional Objectives Appendix A Schedules of Events	Clarified that electrocardiograms are collected to evaluate effect of TAK-573 on QTcF (QT interval corrected by the Fridericia method) intervals (phase 1b and phase 2 safety lead-in); removed reference to prostate cancer; changed antitumor effect assessments to be based on tumor growth rate rather than immune Response Evaluation Criteria in Solid Tumors (iRECIST); added characterization of CD38 receptor occupancy (RO) in the presence of pembrolizumab in patients receiving combination treatment, and evaluation of correlations with clinical outcome with the on-treatment immunophenotype of the tumor microenvironment or changes in the immunophenotype from baseline for patients in phase 2.	Update.
9.	Section 2.0 Study Summary Section 5.2.1 Primary Endpoints Appendix A Schedules of Events	Specified that dose-limiting toxicities (DLTs) and patients with treatment-emergent adverse events (TEAEs), serious adverse events, and TEAEs leading to dose modification or treatment discontinuation are endpoints only for phase 1b and the phase 2 safety lead-in; added overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors v1.1 for phase 2 expansion patients.	Update.
10.	Section 2.0 Study Summary Section 5.2.2 Primary Endpoints Appendix A Schedules of Events	Added maximum tolerated dose/pharmacologically active dose if available from phase1b; added recommended phase 2 dose for SA TAK-573 and in combination with pembrolizumab; specified pharmacokinetic (PK) collection for phase 1b and phase 2 safety lead-in; applies ORR to patients in phase 1b only; specified that efficacy endpoints of disease control rate, duration of response, time to progression, and progression-free survival per mRECIST v 1.1 apply to patients in both phases of study; removed references to prostate cancer and RECIST v 1.1.	Update.
11.	Section 5.2.3 Additional/Exploratory Endpoints Appendix A Schedules of Events	Removed reference to prostate cancer patients; clarified that evaluation of antitumor effect is based on tumor growth rate, not iRECIST; added pembrolizumab PK, cellular CD38 RO, and immunophenotypic evaluation of tumor and tumor microenvironment.	Update.
12.	Section 8.2 Definitions of Dose-Limiting Toxicities	Changed DLT definition of Grade 4 neutropenia from lasting >5 days to lasting >7 days.	Update.

Summary of Changes since the Last Approved Protocol			
Number	**Section(s) Affected by Change**	**Description**	**Rationale**
13.	Section 8.1 Study Drug Administration Section 8.6.3.2 Pembrolizumab Dose Modification Guidelines Section 8.6.4.2 Criteria for Discontinuing Pembrolizumab Appendix A Schedules of Events Section 8.13.2 Pembrolizumab Section 8.15.2 Pembrolizumab Section 10.2.1.2 Pembrolizumab	Added information about pembrolizumab dosing, dose reductions, toxicities, and discontinuing pembrolizumab.	Update.
14.	Section 8.6 Dose Modification Guidelines Appendix A Schedules of Events	Dose modification recommendations for TAK-573 toxicities were revised.	Update.
15.	Section 8.10.1 Infusion-Related Reactions Appendix A Schedules of Events	Expanded and revised information regarding management of infusion-related reactions; added new Section 8.10.3.	Update.
16.	Section 8.8.1 Premedication Appendix A Schedules of Events	Revised recommendations for pre- and posttreatment infusion medications.	Update.
17.	Section 9.3.7 Vital Signs Appendix A Schedules of Events	Added pulse and oxygen saturation to vital signs.	Update.
18.	Section 9.3 Study Procedures Section 9.3.4 Physical Examination Section 9.3.13 Clinical Laboratory Evaluations	Allowed exceptions for alternative methods for conducting patient visits and performing laboratory and imaging assessments during the COVID-19 public health emergency.	Update.
19.	Section 2.0 Study Summary Section 6.2 Number of Patients Section 13.1 Determination of Sample Size	Expected study size is increased to 114 patients.	Update.
20.	Appendix A Schedules of Events	The Schedule of Event tables have been revised and footnotes consolidated to reflect changes in study conduct as detailed above.	Update.
21.	Section 4.3 Known and Potential Benefits and Risks	Updated safety information in Section 4.3 per most recent safety data cutoff (23 January 2021).	Update.
22.	Section 9.3.13.3 Immunosafety Markers Appendix A Schedules of Events	Added immunosafety markers to required laboratory tests.	Update.
23.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria	Added missing glomerular filtration rate cutoff.	Correction.
24.	Section 2.0 Study Summary Section 13.0 Statistical Methods	Statistical methods were revised to include addition of phase 2 portion.	Update.

Summary of Changes since the Last Approved Protocol			
Number	**Section(s) Affected by Change**	**Description**	**Rationale**
25.	Section 9.3.13 Clinical Laboratory Evaluations	Section 9.3.15 PSA was deleted.	Update.
26.	Appendix B PK Sampling Tables	Adjusted PK sampling to align with changes in study design.	Update.
27.	9.3.9 Pregnancy Testing Appendix A Schedules of Events	Frequency and timing of pregnancy testing was updated.	Update

16.9.4 Protocol Amendment 2 Summary of Changes

The changes in the protocol incorporating Amendment 02 are described below. The primary reasons for this amendment were to modify the expansion cohorts, include enrollment and imaging assessment criteria for CRPC patients, include information about a new AESI, and add corticosteroids to the premedication regimen. Minor grammatical, editorial, and formatting changes were included for clarification purposes only.

Changes in Amendment 2

1. Updated clinical safety information.
2. Modified the dose expansion phase to include 8 cohorts with up to 7 patients in each one and changed the expected enrollment size.
3. Included additional information about IRRs.
4. Revised the rationale for the dose expansion cohorts.
5. Defined the dose expansion phase patient population.
6. Increased the expected number of sites.
7. Added a life expectancy requirement to eligibility criteria.
8. Changed the eGFR calculation to the MDRD or CKD-EPI methods.
9. Included enrollment criteria for CRPC patients.
10. Removed plasmapheresis from the list of permitted concomitant medications and procedures.
11. Revised the exclusion criterion for prior treatment.
12. Added an exclusion criterion for persistent toxicity.
13. Clarified criteria for discontinuation of TAK-573.
14. Revised instructions about premedications.
15. Clarified permitted concomitant medications in the Cycle 1 DLT evaluation period in the dose escalation phase.
16. Added detail regarding management of IRRs and recording as an AESI.

17. Defined the imaging schedule for non-CRPC and CRPC patients.
18. Added a new section describing IRRs as AESIs.
19. Added a new section detailing how to report AESIs.
20. Revised the determination of study size to reflect the change in dose expansion cohorts.
21. Removed text about an interim analysis.
22. Removed "Q3W" from the titles of the SOEs.
23. Revised SOE to reflect change in disease assessment guidelines.

16.9.5 Protocol Amendment 1 Summary of Changes

The changes in the protocol incorporating Amendment 01 are described below. The primary reasons for this amendment were to clarify requirements for laboratory and clinical tests, revise dose modification guidelines, and permit corticosteroids. Minor grammatical, editorial, and formatting changes were included for clarification purposes only.

Changes in Amendment 1

1. Removed language permitting administration of corticosteroids.
2. Patients with castration-resistant prostate cancer (CRPC) without visceral disease are excluded from the requirement of fresh biopsy.
3. The window for the use of other investigational products was changed from 30 days to 28 days before first dose.
4. Removed the requirement to use a Holter monitor for electrocardiogram (ECG) testing.
5. Modified the definition of a DLT to include Grade 4 neutropenia lasting >5 days.
6. Revised dose modification recommendations for Grade 3 and Grade 4 adverse events (AEs).
7. Clarified that vital signs may be measured in a supine or semirecumbant position.
8. Removed requirement for antiplatelet antibody testing.
9. Clarified that the laboratory measurement urate can also be measured as uric acid.
10. Added text stating that a separate informed consent form (ICF) will be used to address the possibility of pseudoprogression.
11. Clarified that the definition of a serious adverse event (SAE) includes the signs and symptoms of progressive disease (PD) but does not include the Preferred Term (PT) of disease progression.
12. Added laboratory assessment for blood typing and note for potential blood banks.
13. Limited the number of dose reductions to 2 due to the same AE.
14. Added the measurement of anti–TAK-573 antibody incidence and titer as a secondary endpoint.

15. Modified food intake recommendations to allow some food if necessary.
16. Clarified action of daratumumab on CD38-expressing (CD38+) immune cells.
17. Clarified that pregnancy tests at end of treatment can be urine or serum tests.
18. Added statement that T-cell measurement will include CD4+ and CD8+ T cells.
19. Removed duplication of laboratory tests.
20. Clarified that the blood sample for circulating tumor cells will be collected only during dose expansion.
21. Added contact information for SAE reporting and clarified reporting procedures.
22. Removed needle specifications for tumor biopsies.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	29-Jul-2022 17:15 UTC
[redacted]	Clinical Approval	31-Jul-2022 13:14 UTC
[redacted]	Clinical Approval	01-Aug-2022 13:15 UTC
[redacted]	Clinical Pharmacology Approval	03-Aug-2022 16:24 UTC