Clinical Study Protocol

NCT Number: NCT04381650

Title: A Phase 1b/2 Study of TAK-981 Plus Pembrolizumab to Evaluate the Safety, Tolerability, and Antitumor Activity of the Combination in Patients With Select Advanced or Metastatic Solid Tumors

Study Number: TAK-981-1502

Document Version and Date: Amendment 6, 22 Jun 2023

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

A Phase 1b/2 Study of TAK-981 Plus Pembrolizumab to Evaluate the Safety, Tolerability, and Antitumor Activity of the Combination in Patients With Select Advanced or Metastatic Solid Tumors

Sponsor:	Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 Please note: Takeda Development Center Americas, Inc. (TDC Americas) may be referred to in this protocol as "sponsor" or "Takeda".
Study Number:	TAK-981-1502
EudraCT Number:	2020-004325-23
Compound:	TAK-981
Date:	22 June 2023 **Amendment Number:** 6

Date	Amendment Number	Region
22 June 2023	Amendment 6	Global
01 July 2022	Amendment 5	Global
09 September 2021	Amendment 4	Global
23 April 2021	Amendment 3	Global
10 February 2021	Amendment 2	Global
22 April 2020	Amendment 1	Global
19 February 2020	Original 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.

TDC-Americas–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

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 also 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.

PPD , MD Date
PPD
Oncology Clinical Research

PPD , PhD Date
PPD
(or designee)

PPD , PhD Date
PPD ,
Quantitative Clinical Pharmacology
(or designee)

1.3 Protocol Amendment 6 Summary of Changes and Rationale

Rationale for Amendment 6

This section describes the changes in reference to the protocol incorporating Amendment 6.

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

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0 STUDY SUMMARY Section 6.3 Phase 2–Expansion in Select Indications	Removed small cell lung cancer (SCLC) population. Removed Cohort H.	Reflecting changes in study design, the SCLC population and Cohort H were removed.
2	Section 2.0 STUDY SUMMARY Section 6.3 Phase 2–Expansion in Select Indications	Changed selection and timing of dosing.	Clarification added to reflect changes in study design.
3	Section 2.0 STUDY SUMMARY Section 6.3.1 Early Stopping Rules	Added stopping rules for Cohort F. Removed Cohorts G and H.	Stopping rules updated for Cohort F to reflect change in Cohort F. Cohorts G and H have been removed from the study.
4	Section 2.0 STUDY SUMMARY Section 6.4 Number of Patients Section 13.3 Determination of Sample Size	Updated number of patients.	Number of patients was updated to account for removal of Cohorts G and H, and change for Cohort F.
5	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Added clarification for inclusion criterion #3F that patients with driver mutations are not eligible. Removed criteria #3G and #3H.	Added for clarification. Head and neck squamous cell carcinoma (HNSCC) and microsatellite instability, high levels/mismatch-repair-deficient (MSI-H/dMMR) colorectal cancer (CRC) populations were removed from the study.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Removed exclusion criterion #2.	Palliative radiation in patients on treatment with TAK-981 and pembrolizumab has showed no safety signals, therefore radiation within 4 weeks from cycle 1 day 1 is no longer considered a safety concern.
7	Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Removed Cohorts G and H. Added sample size calculation for Cohort F and clarified that Cohort F will have 2 dose levels.	Cohorts G and H have been removed from the study. Added to provide rationale for sample size calculation in Cohort F.
8	Section 4.1.2 Cervical Cancer	Section updated.	Updated to reflect latest clinical data.
9	Section 4.1.3 Colorectal Cancer	Section updated.	Updated to reflect latest clinical data.
10	Section 4.1.4 Small Cell Lung Cancer	Section removed.	The SCLC population was removed from the study.
11	Section 4.1.5 Head and Neck Squamous Cell Carcinoma	Section removed.	The HNSCC population was removed from the study.
12	Section 4.2.6 Clinical Experience	Section updated.	Updated clinical data from the investigator's brochure (IB) were available.
13	Section 4.3 Pembrolizumab	Updated prescribing information (PI) reference from 2018 to 2023.	Updated to latest PI.
14	Section 4.4 Rationale for the Proposed Study	Updated study rationale.	Study rationale was updated to reflect change in study design.
15	Section 4.5 Rationale for the Proposed Patient Population	Section updated to remove nonsquamous non-small cell lung cancer (NSCLC), SCLC, and MSI-H/dMMR CRC populations.	The removed populations will not be part of the study as of Amendment 6.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16	Section 4.5.1 Rationale for the TAK-981 Starting Dose and Schedule	Section removed.	Rationale for starting dose is no longer necessary given available clinical data.
17	Section 4.5.1 Rationale for the Phase 2 Dose of TAK-981 in TAK-981-1502	Removed reference to Cohorts G and H.	Cohorts G and H have been removed from the study.
18	Section 4.6.2.1 Lymphoid and Hematopoietic Effects	Updated section with latest data to align with IB Edition 5.	Updated to align with IB Edition 5.
19	Section 4.6.3 Potential Effects of TAK-981 Based on TAK-981 Clinical Studies	Updated section with latest data to align with IB Edition 5.	Updated to align with IB Edition 5.
20	Section 4.6.4 Potential Effects of Pembrolizumab	Updated PI reference from 2018 to 2023.	Updated to latest PI.
21	Section 4.6.5 Potential Overlapping Toxicities	Updated PI reference from 2018 to 2023.	Updated to latest PI.
22	Section 6.1 Overview of Study Design	Updated Figure 6.a.	Figure 6.a was updated to reflect changes in study design.
23	Section 6.5 Patient Replacement Section 9.7.2 Patient Replacement	Removed “patients enrolled in Phase 2 will not be replaced”.	Updated to reflect changes in study design.
24	Section 6.6.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures	Updated duration of study.	Changed to align with changes in study design.
25	Section 6.6.4 Total Study Duration	Updated approximate total study duration from 48 months to 60 months.	Changed to align with changes in study design.
26	Section 8.1.1 TAK-981	Updated criteria for patient discharge after study drug administration.	Added as a clarification that in Phase 2 patients can be discharged 1 hour after the administration of study drug.
27	Section 8.1.2 Pembrolizumab	Updated PI reference from 2018 to 2023.	Updated to latest PI.
28	Section 8.5.3 Criteria for Dose Interruption or Dose Reduction	Updated PI reference from 2018 to 2023.	Updated to latest PI.
29	Section 8.5.3.2 Pembrolizumab Dose Modification Guidelines	Updated PI reference from 2018 to 2023.	Updated to latest PI.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
30	Section 9.4.7 Pregnancy Test	Added clarification that screening result for pregnancy must be available and negative before enrollment and dosing.	Added for clarification.
31	Section 9.4.12.1 Clinical Chemistry, Hematology, and Urinalysis	Removed assessment of turbidity and color from urinalysis tests.	Assessment of turbidity and color is not necessary.
32	Section 9.4.13 Disease Assessment	Added PET.	Added for clarification.
33	Section 9.4.14.1 Primary Specimen Collection	Updated Table 9.e.	Plasma collection is mandatory in both Phase 1 and Phase 2.
34	Section 9.4.14.2 Tumor Biopsies	Updated wording for collection of tumor biopsies.	Wording was updated for clarity.
35	Section 9.4.14.4 Fresh Paired Tumor Biopsy	Removed redundant wording for collection of tumor biopsies.	Wording was updated for clarity.
36	Section 9.4.17 DNA Measurements	Clarified wording for assessment of tumor mutations.	Changed for clarification.
37	Section 13.2 Interim Analysis and Criteria for Early Termination	Specified that Cohorts A to F will be examined for overall response rate below the futility boundary.	Specified criteria to stop enrollment.
38	Appendix A Schedule of Events Table 1.b	Added footnote for end-of-treatment visit.	Added for clarification.
39	Appendix A Schedule of Events Table 1.b	Added clarification for footnote p.	Clarification to allow CT scans collected before screening as valid for screening.
40	Appendix A Schedule of Events Table 1.b	Added columns for Cycle 4 and onwards.	Added for clarification.
41	Appendix A Schedule of Events Table 2.b	Added pharmacokinetics (PK) sampling timepoint.	Added to evaluate the robustness of PK results.
42	Appendix A Schedule of Events Table 3.b	Adjusted biomarker sampling.	Adjusted to align with the biomarker sampling schedule.

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 patients 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 defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C 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)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. (TDC Americas)	**Compound**: **TAK-981**
Title of Protocol: A Phase 1b/2 Study of TAK-981 Plus Pembrolizumab to Evaluate the Safety, Tolerability, and Antitumor Activity of the Combination in Patients With Select Advanced or Metastatic Solid Tumors	**EudraCT No.:** 2020-004325-23
Study Number: TAK-981-1502	**Phase:** 1b/2

Study Design:

The study consists of 2 phases, Phase 1b (dose escalation) and Phase 2 (expansion in select indications).

The study will consist of a screening period (Day –28 to −1), a treatment period, an end of treatment (EOT) visit, 2 follow-up visits at 30 and 90 days after the last dose occurring when treatment is discontinued for any reason, and a survival follow-up period lasting for a maximum of 12 months for each patient after their last dose of study drug to monitor disease and survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives TAK-981. One cycle of treatment will be defined as 21 days. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will receive treatment with TAK-981 and pembrolizumab for up to 24 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the study or study drugs occurs. Treatment may be continued beyond disease progression, with sponsor approval, if, in the opinion of the investigator, the patient continues to experience clinical benefit.

Phase 1b: Dose Escalation

The Phase 1b portion of the study is a dose escalation of TAK-981 in combination with pembrolizumab at a fixed dose in patients with nonsquamous non-small lung cancer (NSCLC), cervical cancer, or microsatellite stable colorectal cancer (MSS-CRC). Dose escalation of TAK-981 will be guided by a Bayesian Optimal Interval Design (BOIN) to guide the recommended Phase 2 dose (RP2D) for the combination therapy. The RP2D will be determined from the collective experience in the clinic considering the safety data including the pattern of immune-related adverse event across all patients beyond the dose-limiting toxicity (DLT) window, preliminary pharmacokinetic (PK) data, preliminary pharmacodynamic data, preliminary translational data, and any early antitumor activity observed along with the decision boundaries from the BOIN design.

A safety monitoring committee composed of the principal investigators, and sponsor clinician will regularly review safety data to ensure patients' safety throughout the Phase 1b portion of the study and make decisions on dose escalation.

Phase 2: Expansion in Select Indications

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with pembrolizumab in patients with select cancers. The following cohorts will be enrolled:

- Cohort A: Non-squamous NSCLC.
- Cohort B: Cervical cancer.
- Cohort C: MSS-CRC.
- Cohort D: Cutaneous melanoma.
- Cohort E: Squamous NSCLC.
- Cohort F: checkpoint inhibitor (CPI) refractory squamous or nonsquamous NSCLC.

Enrollment will be initiated in Cohorts A through D. Enrollment to Cohort E will be initiated after positive readouts in Stage 1 from any of Cohorts A through D. Enrollment to Cohort F will be initiated after positive readouts in Stage 1 from any of the lung cancer cohorts (Cohorts A or E).

Cohorts A to E will be assessed separately using an adaptive 2-stage design for a single proportion. For Stage 1,

each cohort will be analyzed when a prespecified number of patients have been enrolled and had the potential to have at least 1 post-treatment scan (ie, after the first disease assessment, 2 months from Cycle 1, Day 1 [C1D1]). Enrollment will be paused at the end of Stage 1 for each arm. If the prespecified minimal response rate is not achieved in the first stage for a given cohort, that cohort will be closed to enrollment. If the required response rate during Stage 1 is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients for that cohort has been reached. The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have had the opportunity to complete the 6-month disease assessment.

The preliminary safety and efficacy of TAK-981 in combination with pembrolizumab in primary refractory NSCLC will be assessed in Cohort F, which includes 2 dose-expansion levels following Simon's 2-stage design. For Stage 1, each cohort will be analyzed when a prespecified number of patients (as defined in Section 13.0) have been enrolled and had the potential to have at least 1 posttreatment scan (ie, after the first disease assessment, 2 months from C1D1). However, in the absence of significant safety signals and conditional to passing the futility analysis in Cohorts A or E, enrollment to Cohort F may continue (up to 15 subjects in each dose level) after the completion of enrollment of Stage1 patients and before response evaluation of these patients. Cohorts A, E, and F are independent study cohorts and will be separately evaluated for efficacy.

In Phase 2, TAK-981 will be evaluated using 2 dose regimens:

- A dose of 90 mg twice weekly (BIW) (a lower biologically active dose; BIW will be on Days 1, 4, 8, and 11) during the first 3 cycles followed by 90 mg weekly (QW) (on Days 1 and 8), both in combination with a fixed dose of pembrolizumab.
- A dose regimen of 120 mg QW (Days 1 and 8) in a 21-day cycle (the highest, safe dose level studied in Phase 1, but with exposures below the maximum tolerated dose [MTD] in the first-in-human Phase 1 study of TAK-981 [120 mg BIW] as a single agent) in combination with a fixed dose of pembrolizumab in patients with NSCLC.

Considering the totality of the data from this study (TAK-981-1502) and factoring in safety, PK, and pharmacodynamics data from the first-in-human single-agent study (Study TAK-981-1002), upon implementation of Amendment 6, TAK-981 dose of 90 mg BIW will be evaluated in Phase 2 expansion Cohorts A to F, while the TAK-981 dose of 120 mg QW will be initially evaluated in Cohorts A and F. Additional cohorts of TAK-981 at 120 mg QW may be opened in the protocol-specified cohorts to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

During Phase 2, an independent data monitoring committee will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

Primary Objectives:

Phase 1b:

- To determine the safety and tolerability of TAK-981 in combination with pembrolizumab in patients with select solid tumor indications.
- To establish the RP2D.

Phase 2:

- To evaluate the preliminary efficacy of TAK-981 at the RP2D in combination with pembrolizumab in patients with select solid tumor indications.

Secondary Objectives:

Phase 1b:

- To characterize the PK of TAK-981 in combination with pembrolizumab.
- To determine the MTD and/or pharmacologically active dose of TAK-981 when administered in combination with pembrolizumab.
- To assess the preliminary antitumor activity of TAK-981-pembrolizumab combination.
- To assess target engagement of TAK-981 (small ubiquitin-like modifier [SUMO]-TAK-981 adduct

formation) and SUMOylation pathway inhibition in blood.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with pembrolizumab in select solid tumors as measured by disease control rate (DCR), durable response rate (DRR), duration of response (DOR), time to response (TTR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).
- To evaluate the safety and tolerability of TAK-981 in combination with pembrolizumab.
- To collect PK data to contribute to population PK and exposure-response (safety/efficacy) analysis.

Patient Population:

Male and female patients, aged 18 years or older with a histologically or cytologically documented, locally advanced or metastatic solid tumors in selected indications will be enrolled.

Number of Patients:	**Number of Sites:**
A total of approximately 231 patients will be enrolled in this study: approximately 32 patients in the Phase 1b dose escalation and approximately 76 to 199 patients in the Phase 2 portion of the study (approximately 9-23 patients for Cohorts A-C, and E, approximately 11-36 patients for Cohort D, and approximately 10-24 for Cohort F).	Estimated total: approximately 60, globally (United States, Canada, Europe, Asia, and South America).
Dose Level(s): Phase 1: The proposed starting dose level for TAK-981 in combination with pembrolizumab for this Phase 1b/2 study will be 40 mg, which is 1 dose level below the monotherapy dose that has cleared the DLT period in the ongoing first in human single-agent study TAK-981-1002. Phase 2: • Cohorts A and F: 90 mg TAK-981 BIW (on Days 1, 4, 8, and 11) or 120 mg TAK-981 QW (on Days 1 and 8) of each 21-day cycle. • Cohorts B, C, D, and E, each: 90 mg TAK-981 BIW (on Days 1, 4, 8, and 11) of each 21-day cycle. Patients on the TAK-981 BIW schedule in combination with pembrolizumab 200 mg every 21 days will be treated with an induction treatment period of at least 3 cycles with the BIW schedule, followed by the QW schedule.	**Route of Administration:** TAK-981: Intravenous (IV) Pembrolizumab: IV
Duration of Treatment: Treatment with TAK-981 with pembrolizumab will be administered for up to 24 months or until patients meet any of the discontinuation criteria.	**Period of Evaluation:** The expected period of evaluation for this study is 48 months; approximately 24 months for enrollment and approximately 24 months for treatment and/or follow-up.

Main Criteria for Inclusion:

1. Adult male or female patients aged 18 years or older.
2. Be willing and able to provide written informed consent for the study.
3. Have a histologically or cytologically documented, advanced (metastatic and/or unresectable) cancer as listed below that is incurable:

   Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line standard of care treatment unless such treatments were completed less than 12 months prior to the current tumor recurrence.

   A. Non-squamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed and that has progressed on no more than 1 prior systemic therapy. In Phase 2, patients with nonsquamous NSCLC must have not received more than 1 prior systemic therapy and must not have presented with disease progression during the first 6 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy.

      Note: In Phase 1, patients with nonsquamous NSCLC and known driver mutations/genomic aberrations (eg, *EGFR*, B-Raf proto-oncogene mutation V600E [*BRAF* V600E], and ROS proto-oncogene 1 [*ROS1*] sensitizing mutations, neurotrophic receptor tyrosine kinase [*NRTK*] gene fusions, and *ALK* rearrangements) must have also shown progressive disease after treatment with a commercially available targeted therapy. In Phase 2, patients with driver mutations are not eligible.

   B. CPI-naïve cervical cancer (squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix) patients for whom prior standard first-line treatment has failed and who have received no more than 1 prior systemic line of therapy for recurrent or Stage IVB cervical cancer.

      Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric-type adenocarcinoma, clear-cell carcinoma, and mesonephric carcinoma. Histologic confirmation of the original primary tumor is required via pathology report.

      Note: First-line treatment must have consisted of platinum-containing doublet. Chemotherapy administered concurrently with primary radiation (eg, weekly cisplatin) is not counted as a systemic chemotherapy regimen.

   C. CPI-naïve MSS-CRC patients for whom prior standard first-line treatment has failed and who have progressed on/after no more than 3 chemotherapy regimens/lines.

      Note: Patients must have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens if indicated.

   D. Unresectable Stage III or Stage IV cutaneous melanoma that has not received prior therapy in the metastatic setting.

      Note: Patients with acral melanoma are not eligible. Patients who have presented with disease relapse after ≥6 months of the last dose of CPI or BRAF-MEK inhibitor in the adjuvant setting are eligible.

   E. Squamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed. Patients must have not received more than 1 prior systemic therapy and must not have presented with disease progression during the first 6 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy.

   F. Squamous or nonsquamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed within 6 months from the initiation of the CPI. Patients must have not received more than 1 prior systemic therapy in the metastatic setting.

      Note: patients with driver mutations are not eligible.

4. Have at least 1 radiologically measurable lesion based on RECIST, Version 1.1. Tumor lesions situated in a

previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

5. Patients in Phase 2 expansion cohorts must have a PD-L1 result in tumor tissue obtained from an FDA-approved, or Conformité Européene (CE)-marked, or locally equivalent PD-L1 test.
6. Willing to consent to mandatory pretreatment fresh tumor biopsy for Phase 2.

   Note: Pretreatment fresh tumor biopsy at screening can be replaced by a recent (≤12 months old) formalin-fixed, paraffin-embedded tumor specimen. For fresh tumor biopsies, the lesion must be accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal space, or those obtained with endoscopic procedures beyond the stomach or bowel).
7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
8. Demonstrate adequate organ function as described below:
   A. Platelet count $\geq 75.0 \times 10^9$/L.
   B. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.
   C. Hemoglobin ≥85 g/L (red blood cell [RBC] transfusion allowed ≥14 days before assessment).
   D. Calculated creatinine clearance ≥30 mL/min using the Cockcroft-Gault formula.
   E. Aspartate aminotransferase (AST, GOT) and alanine aminotransferase (ALT, GPT) ≤3.0 times the upper limit of normal (ULN), <5.0 times the ULN if liver enzyme elevations are due to liver metastases; bilirubin ≤1.5 times the ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 times the ULN, per discussion between the investigator and the medical monitor.
9. Left ventricular ejection fraction (LVEF) ≥40%; as measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan.
10. Have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.

    Note: Neuropathy Grade ≤2, any grade alopecia, or autoimmune endocrinopathies with stable replacement therapy are permitted.
11. Women of childbearing potential must have a negative serum/urine pregnancy test within 72 hours prior to receiving the first dose of study medication.
12. Female patients must meet 1 of the following:
    A. Postmenopausal for at least 1 year before the screening visit, or
    B. Surgically sterile, or
    C. If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form through 6 months after the last dose of study, or
    D. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)
13. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:
    A. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
    B. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)
14. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

Main Criteria for Exclusion:

1. Received treatment with systemic anticancer treatments or investigational products within 14 days before the first dose of study drug or 5 half-lives, whichever is shorter.

   Note: Low-dose steroids (oral prednisone or equivalent ≤10 mg per day), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed.

2. History of uncontrolled brain metastasis (evidence of progression by imaging over a period of 4 weeks and/or neurologic symptoms that have not returned to baseline). Patients with treated brain metastases are allowed provided they are radiologically stable, without evidence of progression for at least 4 weeks by repeat imaging, clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. Note: For asymptomatic patients, screening brain imaging is not required.
3. Second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy.
4. Major surgery ≤14 days from the first dose of study drug and not recovered fully from any complications from surgery.
5. Prior treatment with TAK-981.
6. Hypersensitivity to TAK-981, pembrolizumab, or any component of the drug product.
7. Baseline prolongation of the QT interval corrected using Fridericia's formula (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
8. History of immune-related AEs related to treatment with immune CPIs that required treatment discontinuation.
9. Receiving or requires the continued use of medications that are known to be strong or moderate inhibitors and inducers of cytochrome P-450 (CYP) CYP3A4/5 and strong P-glycoprotein (Pgp) inhibitors. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and Pgp inhibitors) before receiving a dose of TAK-981.
10. Receipt of any live vaccine within 4 weeks of initiation of study treatment.
11. History of autoimmune disease requiring systemic immunosuppressive therapy with daily doses of prednisone >10 mg/day or equivalent doses, or any other form of immunosuppressive therapy. Hormone replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for thyroid, adrenal or pituitary insufficiency) for endocrinopathies are not considered prohibited forms of systemic treatment of an autoimmune disease.
12. History of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
13. Has evidence of active, noninfectious pneumonitis.
14. History of allogeneic tissue or solid organ transplant.
15. Has active infection requiring systemic therapy.
16. Known history of HIV infection or any other relevant congenital or acquired immunodeficiency.
17. Known hepatitis B virus surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
18. History of any of the following ≤6 months before first dose: congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, unstable symptomatic ischemic heart

disease, uncontrolled hypertension despite appropriate medical therapy, ongoing symptomatic cardiac arrhythmias >Grade 2, pulmonary embolism or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). Chronic atrial fibrillation on stable anticoagulant therapy is allowed.

19. 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.

20. Female patients who are pregnant or lactating and breastfeeding.

Main Criteria for Evaluation and Analyses:

Primary:

Phase 1b:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, except cytokine release syndrome (CRS) that will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS.
- Occurrence of dose-limiting toxicities (DLTs) within the first 21 days of treatment in Cycle 1.

Phase 2:

- Overall response rate (ORR) (CR + PR) as assessed by the investigator according to RECIST, Version 1.1).

Secondary:

Phase 1b:

- ORR, DCR, DRR, DOR, TTR, TTP, and PFS as assessed by the investigator according to RECIST, Version 1.1 and the RECIST consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials (iRECIST).
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood.
- TAK-981 plasma concentration-time data.

Phase 2:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0, except CRS that will be graded according to ASTCT Consensus Grading for CRS.
- DCR, DRR, DOR, TTR, TTP, PFS, and OS as assessed by the investigator according to RECIST, Version 1.1 and iRECIST; ORR as assessed by the investigator according to iRECIST.

Statistical Considerations:

Dose Escalation Phase (Phase 1b):

The BOIN design will be implemented for dose escalation phase. Approximately 4 patients will be initially enrolled in the first cohort.

It is estimated that up to approximately 32 DLT-evaluable patients will be enrolled in this study for the dose escalation phase to evaluate dose escalation for 2 dosing schedules of TAK-981 (ie, Days 1, 4, 8, and 11 or Days 1 and 8 in 21-day cycles).

Efficacy Evaluation Phase (Phase 2):

After select Phase 2 doses are identified, up to approximately 199 response-evaluable patients with select indications and dose levels in 8 cohorts will be enrolled in the Phase 2 study to evaluate the antitumor efficacy of the combination of TAK-981 and pembrolizumab.

The primary endpoint for the Phase 2 portion is ORR (CR + PR) as assessed by the investigator according to RECIST, Version 1.1. The sample size consideration for Cohorts A through E is an adaptive design based on

Simon's 2-stage design for a single proportion with the specified hypotheses of ORR. The sample size consideration for cohort F is a standard Simon's 2-stage design.
Sample Size Justification: It is anticipated that approximately 231 patients will be enrolled in this study, including the Phase 1b portion dose escalation phase and the Phase 2 preliminary evaluation of the antitumor efficacy of the combination at the select Phase 2 doses in patients with select advanced or metastatic solid tumors, such as NSCLC, cervical, MSS-CRC, and melanoma.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Coordinating 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 and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
BOIN	Bayesian Optimal Interval Design
BRAF V600E	B-Raf proto-oncogene mutation V600E
BIW	twice weekly
C1D1	Cycle 1, Day 1
cfDNA	cell-free DNA
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P-450
DC	dendritic cell
DCR	disease control rate
DLT	dose-limiting toxicity
dMMR	mismatch-repair-deficient
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
FDA	Food and Drug Administration
FIH	first-in-human

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	hazard ratio
iCD	immune confirmed progressive disease
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune-confirmed progressive disease
iCR	immune complete response
IDMC	independent data monitoring committee
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IP-10	interferon gamma-induced protein 10
iPR	immune partial response
irAE	immune-related adverse event
IRB	institutional review board
IRC	independent review committee
iRECIST	consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials
IRR	infusion-related reaction
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MSI-H	microsatellite instability, high levels
MSI-L	microsatellite instability, low levels
MSS-CRC	microsatellite stable colorectal cancer
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NK	natural killer
NLNT	new lesion-non-target
NLT	new lesions-target
NRTK	neurotrophic receptor tyrosine kinase
NSCLC	non-small cell lung cancer
ORR	overall response rate

OS	overall survival
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1 [PD-L2]	programmed cell death protein 1 ligand [programmed cell death protein 2 ligand]
PET	positron emission tomography
PFS	progression-free survival
Pgp	P-glycoprotein
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PR	partial response
PRR	pattern recognition receptor
QTcF	QT interval corrected using Fridericia's formula
QW	once weekly
RANKL	receptor activator of nuclear factor kappa-B ligand
RANTES	regulated upon activation normal T-cell expressed and secreted
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	ROS proto-oncogene 1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SMC	safety monitoring committee
SmPC	Summary of Product Characteristics
SOE	schedule of events
SUMO	small ubiquitin-like modifier
TEAE	treatment-emergent adverse event
TME	tumor microenvironment
TTP	time to progression
TTR	time to response
UBC9	ubiquitin carrier protein 9
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Solid Tumors

Immuno-oncology has emerged as the major driver of anticancer therapeutics in both solid tumors and hematologic malignancies. Clinical data from immune checkpoint inhibitors (CPIs) such as CTLA-4 and programmed cell death protein 1 (PD-1)/PD-L1 (PD-1 ligand) inhibitors have changed the therapeutic paradigm in a growing number of indications. Overcoming T-cell inhibition in the tumor microenvironment (TME) with CPIs has proven to be a successful strategy to produce long-term benefit in a significant number of patients with metastatic solid tumors.

However, despite these advances, many advanced cancer patients are either refractory to CPIs or relapse after a period of tumor control, eventually succumbing to their disease. Some predictive biomarkers of CPI response (PD-L1 expression, microsatellite instability, or tumor mutational burden) have been clinically validated, but it remains incompletely understood why most human tumors do not respond to CPIs. Evolving data suggest that reduced interferon (IFN) signaling, immune escape through human leukocyte antigen loss, as well as altered antigen presentation may contribute to CPI resistance (Jenkins et al. 2018; Minn and Wherry 2016; Sharma et al. 2017). Furthermore, an emerging consensus acknowledges that CPI resistance (relapse or refractory in nature) may also be driven by tumor immunophenotype, specifically those tumors harboring an immunosuppressive or “immune desert” phenotype.

Accordingly, one possible strategy to overcome these elements of resistance is to stimulate innate immune cells (myeloid cells including antigen-presenting dendritic cells [DCs], granulocytes, eosinophils, neutrophils, or monocytes/macrophages, as well as lymphoid cells including gamma/delta T-cells, natural killer [NK] cells, and NK T-cells) to condition the TME, thus turning a “cold” tumor into a “hot” tumor in which adaptive immune responses can be effectively activated.

Type I IFNs, such as IFNα and IFNβ are potent immunomodulatory cytokines induced early in the innate immune response which act upon multiple cell types to mold both innate and adaptive immunity. They directly enhance NK cell cytotoxicity and stimulate interleukin (IL)-15 production by DCs to promote NK cell activation (Lee et al. 2000; Lucas et al. 2007). They also directly act upon T-cells to stimulate survival, clonal expansion, and the development of T-cell effector function (Curtsinger et al. 2005; Marrack et al. 1999). Importantly, Type I IFNs play a central role in propagating adaptive immune responses by promoting maturation of DCs and cross-presentation of antigens to T-cells (Diamond et al. 2011; Fuertes et al. 2011). Indeed, innate immune responses have been implicated in tumor surveillance via sensing of tumor DNA through the pattern recognition receptor (PRR) pathway (Woo et al. 2014), activation of which induces production of Type I IFNs, and propagation of an adaptive antitumor response as described above.

4.1.1 Lung Cancer

Lung cancer is the leading cause of cancer-related mortality worldwide, with 142,670 deaths estimated in 2019 in the United States (US) (Siegel et al. 2019). More than 80% of lung cancers are classified as non-small cell lung cancer (NSCLC). Although targeted therapies have redefined treatment options for patients with molecularly defined locally advanced or metastatic NSCLC (eg, epidermal growth factor receptor [EGFR]-mutant, anaplastic lymphoma kinase [ALK]-rearranged NSCLC), these therapies are ineffective in those whose tumors lack such genetic alterations, who comprise the majority of NSCLC patients. However, immunotherapy has become integrated into the first-line treatment of such patients, which has led to improvements in survival. However, despite the overall survival (OS) benefit of CPI in NSCLC, the advanced disease is incurable and will eventually progress. In the Phase 1b KEYNOTE-001 trial of pembrolizumab in patients with advanced NSCLC, the 5-year OS rate in treatment-naive patients with PD-L1 expression ≥50% was 29.6%, 15.7% if PD-L1 was <50%. In patients previously treated whose PD-L1 expression levels were ≥50%, 1% to 49% and <1%, the 5-year OS rate was 25%, 12.6% and 3.5%, respectively.

The introduction of frontline immunotherapy has changed previous treatment paradigms in NSCLC. In patients whose tumors progressed after CPI-based therapy, the choice of treatment with platinum-doublets or docetaxel depends on the chemotherapy regimen associated to the CPI in frontline therapy. Treatment with docetaxel plus ramucirumab in second-line therapy shows an overall response rate (ORR) of 23%, median progression-free survival (PFS) of 4.5 months (hazard ratio [HR]: 0.76, 95% CI, 0.68-0.86), and median OS of 10.5 months (HR: 0.86, 95% CI 0.75-0.98) (Garon et al. 2014). Combination of CPI with the activation of the Type I IFN pathway may reinvigorate the pre-existing immune response and initiate a new antitumor immune response, and it has the potential to improve outcomes in NSCLC including patients with negative PD-L1 expression tumors.

4.1.2 Cervical Cancer

Cervical cancer is the fourth leading cause of cancer-related mortality in women worldwide, with 13,170 new cases and 4250 deaths in 2019 in the US (Siegel et al. 2019). In contrast to patients with early-stage cervical cancer, the prognosis of patients with recurrent or metastatic disease is poor. Over the past 30 years, cisplatin-based combination chemotherapy has been shown to produce the best PFS and median OS: 5 months and 10 to 13 months, respectively (Long et al. 2005; Monk et al. 2009; Moore et al. 2004). The addition of bevacizumab to standard first-line chemotherapy significantly improved median PFS (8.2 vs 5.9 months; HR: 0.67, 95% CI, 0.54-0.82) and median OS (17.0 vs 13.3 months; HR: 0.71, 95% CI, 0.54-0.95) compared with chemotherapy alone. More recently, the anti-PD-1 monoclonal antibody (mAb) pembrolizumab, has received approval for treatment of patients with persistent or recurrent cervical cancer whose tumors express PD-L1 (combined positive score ≥1) either in first line of the metastatic setting in combination with chemotherapy with or without bevacizumab, or as a single agent in the second line.

Combinations with pembrolizumab to reinvigorate the preexisting CD8 effector population plus the initiation of a novel immune response may translate into a significantly higher ORR and a greater clinical benefit.

4.1.3 Colorectal Cancer

Colorectal cancer (CRC) is the second-leading cause of cancer death worldwide, with 51,020 deaths estimated during 2019 in the US (Siegel et al. 2019). Advanced Stage IV metastatic disease is the initial presentation in approximately 25% of patients with CRC, and a further 25% to 50% present with early-stage disease but go on to develop metastatic disease. Despite the development of several chemotherapy regimens and the addition of EGFR/ vascular endothelial growth factor A (VEGFA)-directed mAbs, the prognosis for patients with metastatic CRC remains poor, with a median 5-year survival of only 12.5% in the US (Siegel et al. 2014).

Unfortunately, current CPIs are ineffective in tumors that are mismatch-repair-proficient and microsatellite stable or have low levels of microsatellite instability (MSI-L). In these tumors, low tumor mutation burden and the lack of immune cell infiltration have been posited as mechanisms of immune resistance. Once the tumor has progressed to mAb-based chemo regimens, the 2 available therapeutic options, regorafenib and trifluridine-tipiracil, have shown poor ORR (1.6% to 3%), with median PFS and median OS of 2 and 7 months, respectively (Mayer et al. 2015; Van Cutsem et al. 2012).

4.1.4 Cutaneous Melanoma

The worldwide incidence of melanoma has risen rapidly over the course of the past few decades. About 100,350 new cases and 6850 deaths are expected in 2020 in the US (Siegel et al. 2020).

Two cytokines have shown evidence of the activity in melanoma. IFNα2b was approved by the FDA in the adjuvant setting in patients with high-risk malignant melanoma, and high-dose interleukin-2 (IL-2) in patients with metastatic melanoma. More recently, ipilimumab, nivolumab, the combination of both agents, and pembrolizumab have been approved by the FDA for the adjuvant treatment of melanoma patients.

In the metastatic setting, CPIs as single agents, the combination of nivolumab and ipilimumab or nivolumab and relatlimab, and the combination of an MAPK inhibitor with the anti-PD-L1 atezolizumab have been approved for treatment of unresectable Stage III or Stage IV melanoma. The Phase III KEYNOTE-006 trial conducted in patients with advanced melanoma naïve to immunotherapy, has shown improved median OS (33 months vs 16 months), median PFS (8.4 months vs 3.4 months) and higher ORR (42% vs 17%), for pembrolizumab compared with ipilimumab (Robert et al. 2019; Robert et al. 2015; Schachter et al. 2017). However, despite the remarkable improvement in survival, the prevailing unmet needs in first-line unresectable or metastatic malignant melanoma therapies still consolidate around the improvements in efficacy, creating a significant clinical opportunity to extend patients' lives.

4.2 TAK-981

4.2.1 Protein SUMOylation Biology in Cancer

SUMOylation is a post-translational modification that attaches a small ubiquitin-like modifier (SUMO) protein to protein substrates, regulating their activity, subcellular localization, and stability (Geiss-Friedlander and Melchior 2007; Oken et al. 1982). There are 3 functional mammalian paralogues of the SUMO proteins: small ubiquitin-like modifier 1 (SUMO1), small ubiquitin-like modifier 2 (SUMO2), and small ubiquitin-like modifier 3 (SUMO3) (Gareau and Lima 2010; Geiss-Friedlander and Melchior 2007), which are attached to their substrate proteins as monomers (SUMO1) or poly-SUMO chains (SUMO2/3). The SUMOylation process is mediated by an enzymatic cascade similar to that described for ubiquitination (Geiss-Friedlander and Melchior 2007; Seeler and Dejean 2017). An E1 activating enzyme consisting of a SUMO-activating enzyme subunit 1/SUMO-activating enzyme subunit 2 heterodimer binds SUMO, generating a SUMO-SUMO-activating enzyme subunit 2 thioester that is transferred to SUMO-conjugating enzyme (ubiquitin carrier protein 9 [UBC9]), the sole E2 conjugating enzyme in the pathway. SUMO is then covalently attached to a lysine residue on target proteins by an E3 ligase. TAK-981 interrupts this cascade by forming a covalent adduct with SUMO, preventing its transfer from SUMO-activating enzyme to UBC9.

SUMOylation has been reported to regulate cellular processes important for tumor cell proliferation and survival (Gareau and Lima 2010; Geiss-Friedlander and Melchior 2007; He et al. 2017; Seeler and Dejean 2017). In addition, SUMOylation has been reported to play a key role in the regulation of Type I IFN signaling and the innate immune response by transcriptional repression of Type I IFNs, such that inhibiting SUMOylation by genetic means resulted in enhanced basal expression levels and sensitization of induction of Type I IFNs, promoting enhanced innate immune responses to pathogenic stimuli (Crowl and Stetson 2018; Decque et al. 2016).

Initiation of a Type I IFN response represents a strategy for modulating the cancer immunity cycle at its inception, differentiated from the currently approved immuno-oncology therapies, the immune CPIs, which function to disinhibit cytotoxic T-cell activity at more distal parts of the cycle (Chen and Mellman 2013). The full potential of leveraging Type I IFN responses to stimulate antitumor immunity has yet to be realized. Direct systemic administration of IFNα is hampered by serious clinical toxicity. Alternative strategies to induce Type I IFN by stimulating the PRR pathway through administration of agonists (such as stimulator of IFN genes protein [STING] or toll-like receptor agonists) have been largely limited to delivery by intratumoral injection, or topical application, indicative of toxicities associated with systemic administration (Adams 2009). Inhibition of SUMOylation represents a novel therapeutic strategy for initiating Type I IFN responses and promoting antitumor immune responses.

4.2.2 Mechanism of Action

TAK-981 is a first-in-class small molecule inhibitor of SUMOylation. Biochemical and cell-based assays demonstrated that TAK-981 is a potent and selective mechanism-based inhibitor of SUMO-activating enzyme that inhibits SUMOylation by forming a covalent adduct

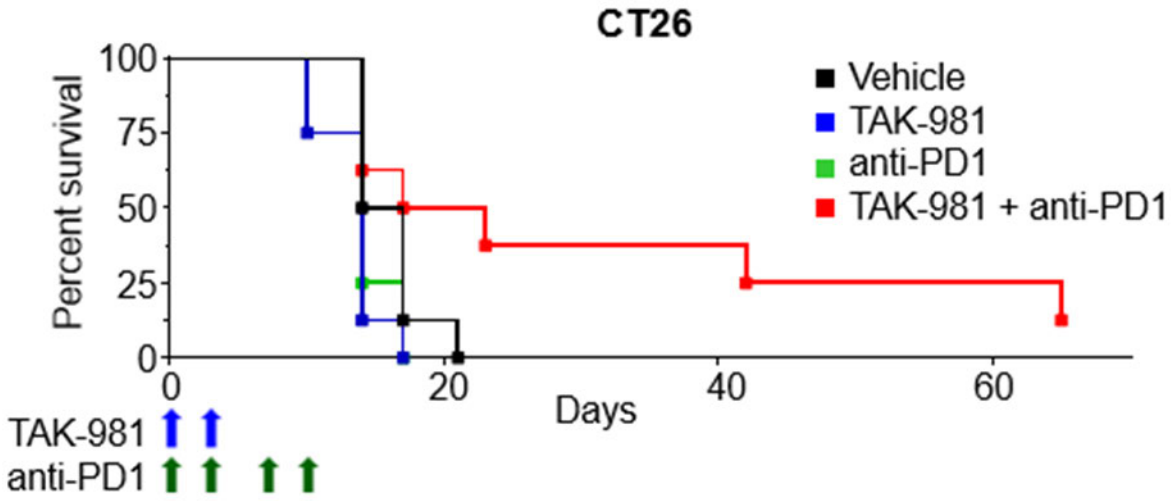
with SUMO when it is bound to SUMO-activating enzyme. Central to the antitumor mechanism of action of TAK-981 is its ability to induce expression of the potent immunomodulatory molecules Type I IFNs. Ex vivo assays demonstrated that TAK-981 promoted the activation of DCs, NK cells, and macrophages in a Type I IFN-dependent manner. In both mouse and human NK cells, TAK-981 promoted upregulation of the T-cell costimulatory markers CD40, CD80, and CD86, as well as production of inflammatory cytokines. In vivo vaccination studies with ovalbumin protein demonstrated enhancement of antigen cross presentation and T-cell priming by TAK-981. In vivo antitumor activity in a mouse syngeneic A20 tumor model was shown to be fully dependent on Type I IFN signaling and capable of generating CRs (defined as the absence of palpable tumor) dependent on the presence of CD8+ T-cells. CRs were resistant to re-challenge with the same (A20) but not a different (CT26) tumor, indicative of a tumor-specific protective immune response.

A pharmacodynamic study assessing the response of lymphocyte populations in circulation and in lymphoid organs after TAK-981 administration to immune-competent BALB/c mice demonstrated depletion of B lymphocytes in the blood, spleen, and lymph nodes. T lymphocyte numbers were also decreased in the blood and spleen within 24 hours of treatment, but showed a marked trend toward an increase in the lymph nodes, indicative of a TAK-981-mediated T-cell redistribution from the periphery to the lymph nodes, consistent with previous observations of Type I IFN-induced T-cell redistribution (Gresser et al. 1981; Kamphuis et al. 2006; O'Neil et al. 2017; Shiow et al. 2006).

4.2.3 TAK-981 in Combination With Checkpoint Inhibitors

Combination with immune CPIs demonstrated enhanced antitumor responses in the CT26 (combination with anti-PD-1) (Figure 4.a) and MC38 (combination with anti-CTLA4) (Figure 4.b) tumor models. In the CT26 tumor model, which did not show single-agent responsiveness to either TAK-981 or an anti-mouse PD-1 antibody, combination treatment resulted in a significant survival benefit relative to either single-agent treatment. Flow cytometry analysis revealed that those CT-26 tumors exhibiting marked growth inhibition in response to treatment with the TAK-981 and anti-PD-1 combination showed enhanced activation of CD8+ T-cells and NK cells compared to vehicle or single-agent treated tumors.

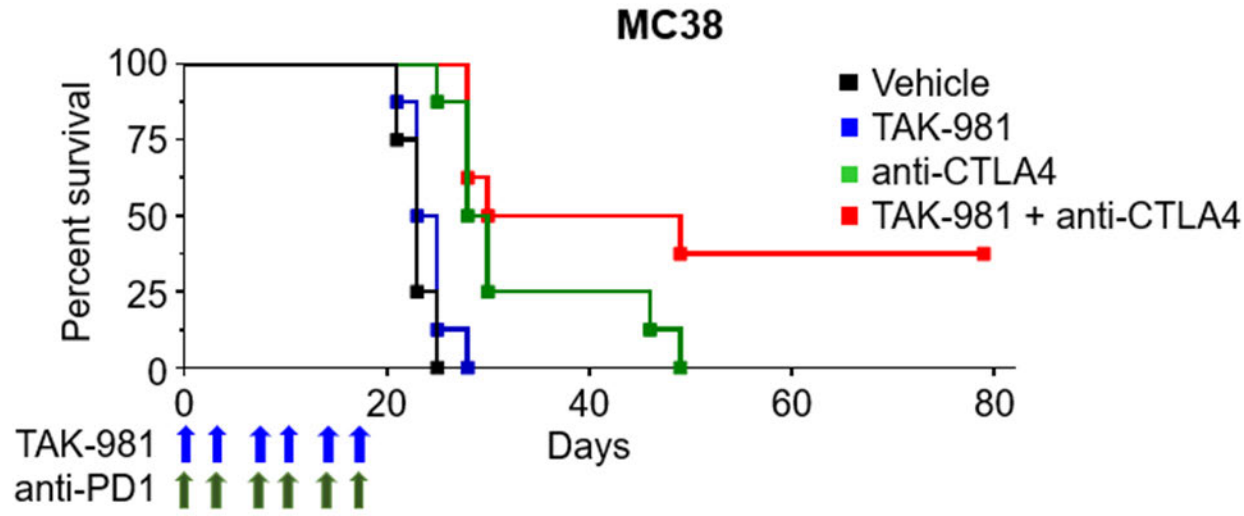
Figure 4.a Survival Curves for the Combination of TAK-981 With Anti-PD-1 Antibody



PD-1: programmed cell death protein 1.

BALB/c mice inoculated subcutaneously with CT26 tumor cells were treated with vehicle on Days 0, 3, 7, and 10, or with 7.5 mg/kg TAK-981 on Day 0 and 3 (blue arrows), or with 10 mg/kg anti-mouse PD-1 antibody on Days 0, 3, 7, and 10 (green arrows), or with a combination of TAK-981 (Day 0 and 3) and anti-PD-1 antibody (Days 0, 3, 7, and 10). The combination of TAK-981 with anti-PD-1 resulted in significantly improved survival relative to either single-agent treatment ($p < 0.001$). P-values were calculated by Weibull regression analysis.

Figure 4.b Survival Curves for the Combination of TAK-981 With Anti-CTLA4 Antibody



C57BL/6 mice inoculated subcutaneously with MC38 tumor cells were treated with vehicle, TAK-981 (blue arrows), anti-mouse CTLA4 antibody (olive green arrows) or TAK-981 combined with anti-mouse CTLA4 on Days 0, 3, 7, 10, 14, and 17. The combination of TAK-981 with anti-CTLA4 resulted in significantly improved survival relative to TAK-981 alone ($p < 0.001$) or anti-CTLA4 alone ($p = 0.0019$). P-values were calculated by Weibull regression analysis.

4.2.4 Nonclinical Pharmacokinetics

TAK-981 has an acceptable nonclinical pharmacokinetic (PK) profile for continuing evaluation and development in humans.

- In plasma, after single intravenous (IV) administration, TAK-981 showed moderate to high plasma clearance and volume of distribution at steady state (V_{ss}) after IV administration in mice, rats, dogs, and monkeys with half-lives varying from 2 to 6 hours among species.

4.2.5 Nonclinical Toxicology

The nonclinical toxicology profile of TAK-981 has been fully characterized in a comprehensive toxicology program that included single- and repeat-dose studies in rats and dogs. Repeat daily dosing resulted in unacceptable toxicity due to multiorgan failure in rats and fever (increased body temperature) in dogs. Increased body temperature was observed in dogs after a single dose of TAK-981 at ≥3 mg/kg and was dose limiting at 12 mg/kg with body temperature reaching up to 40.3ºC (compared to baseline body temperature of 37.8ºC to 38.9ºC). Increased body temperature (0.5°C to 2.0°C) was also observed in dogs at ≥3 mg/kg in a single-dose cardiovascular assessment study and after repeat once-daily or once-weekly (QW) dosing. Increased body temperature in the cardiovascular assessment study was not associated with effects on blood pressure or electrocardiogram (ECG) morphology but was associated with increased heart rate. Because intermittent dosing on a QW or twice-weekly (BIW) schedule was demonstrated to be efficacious in mouse models, both QW and BIW schedules were examined in Good Laboratory Practices (GLP) toxicology studies. Once per week dosing (5 doses) was associated with multiorgan failure in rats at ≥20 mg/kg, but was well tolerated in dogs up to the top dose of 6 mg/kg. However, twice-weekly dosing (4 doses) was well tolerated in both species up to the top dose of 10 mg/kg in rats and 4 mg/kg in dogs. In the Phase 1 clinical trial, patients have been dosed on either a QW or BIW schedule.

The primary toxicity with BIW dosing was dose-dependent mild to marked decreases in peripheral blood lymphocyte counts that affected T cells, T-cell subsets (helper, cytotoxic, activated, memory, regulatory), B cells, and NK cells approximately equally. Decreases in lymphocyte count were associated with decreases in lymphoid cellularity in the primary and secondary lymphoid organs including the thymus, spleen, lymph nodes, and gut-associated lymphoid tissue. Decreases in other circulating cell types including neutrophils, monocytes, basophils, and/or eosinophils were also observed, but were of decreased severity compared to decreases in lymphocyte counts. Additional effects observed with twice-weekly dosing were limited to myeloid hyperplasia in the bone marrow in rats at 10 mg/kg and in dogs at 4 mg/kg; modest increases in serum monocyte chemotactic protein-1 (MCP-1), IFN gamma-induced protein 10 (IP-10) (rats only), and RANTES (regulated upon activation normal T-cell expressed and secreted) (rats only) at ≥0.5 mg/kg (with no increases in cytokines typically associated with cytokine release syndrome [CRS]); injection site reactions in rats at ≥0.5 mg/kg; single-cell necrosis in the stomach in dogs at ≥2 mg/kg; and renal pelvis inflammation and fibrinoid vascular necrosis (without involvement of the renal parenchyma or alterations in renal parameters) in dogs at 4 mg/kg. Additional TAK-981-related effects after repeat daily or

once-weekly dosing, often at nontolerated doses only, were observed in the bone marrow, liver, kidney, urinary bladder (dog only), gastrointestinal tract, heart, musculoskeletal system, lung (rat only), endocrine system (rat only), glandular organs (rat only), and reproductive tract (rat only). All target organ toxicities at tolerated doses were considered to be monitorable, except for inflammation and vascular necrosis in the renal pelvis in dogs. All target organ toxicities were completely or partially reversible.

An in vitro cytokine release assay was performed to evaluate the risk of TAK-981 to produce clinically significant CRS, and results were considered negative. TAK-981 was not mutagenic in a GLP-compliant Ames assay; however, TAK-981 was associated with genotoxicity at ≥5 mg/kg in an in vivo micronucleus assay in rats and was clastogenic in an in vitro chromosomal aberration assay with human peripheral blood lymphocytes. Reproductive and developmental toxicity studies have not been conducted; however, there were no TAK-981–related reproductive findings in rats or dogs with BIW dosing or in dogs with QW dosing. In the rat study with QW dosing, there were partially to fully reversible microscopic findings in reproductive tissues; in a non–GLP-compliant 7-day repeat-dose toxicity study in male rats, there were microscopic and organ weight changes in reproductive tissues in animals that had significant systemic toxicity. TAK-981 did not demonstrate phototoxic potential in an in vitro assay.

4.2.6 Clinical Experience

TAK-981 is being evaluated in 4 clinical studies: 1 first-in-human (FIH) Phase 1/2 study in patients with advanced or refractory solid tumors or lymphomas (Study TAK-981-1002), 1 Phase 1/2 clinical study in combination with rituximab in patients with relapsed/refractory indolent or aggressive CD20+ non-Hodgkin lymphomas (Study TAK-981-1501), 1 Phase 1b/2 clinical study in combination with pembrolizumab in patients with select advanced or metastatic solid tumors (Study TAK-981-1502), and 1 Phase 1b/2 study in combination with anti-CD38 monoclonal antibodies in adult patients with relapsed/refractory multiple myeloma (Study TAK-981-1503).

As of the 28 June 2022 data cutoff for the investigator's brochure (IB), 194 patients have been treated with TAK-981 across 4 clinical trials; 92 patients have received single agent TAK-981, and 102 patients have received TAK-981 as part of a combination regimen. Overall, TAK-981 has been well tolerated, and the type of treatment-emergent adverse events (TEAEs) are consistent with induction of interferon signaling or were consistent with the patients' underlying cancer disease (see Section 4.6.2 and Section 8.9 for more details). The most common TEAEs (>20%) in the total population in Studies TAK-981-1002, TAK-981-1501, TAK-981-1502, and TAK-981-1503 are fatigue, pyrexia, nausea, diarrhoea, chills, headache, vomiting, decreased appetite, anaemia, and dyspnoea (Table 4.a). Overall, preliminary efficacy is being observed, and efficacy evaluations are ongoing. (Refer to current TAK-981 IB for details).

Table 4.a Most Frequent (≥10% of All Patients) TEAEs in Studies TAK-981-1002, TAK-981-1501, TAK-981-1502, and TAK-981-1503

Preferred Term	Number of Patients (%) Total (N = 194)
Fatigue	90 (46.4)
Pyrexia	79 (40.7)
Nausea	70 (36.1)
Diarrhoea	67 (34.5)
Chills	65 (33.5)
Headache	59 (30.4)
Vomiting	50 (25.8)
Decreased appetite	49 (25.3)
Anaemia	42 (21.6)
Dyspnoea	39 (20.1)
Hypokalaemia	36 (18.6)
Arthralgia	33 (17.0)
Abdominal pain	31 (16.0)
Back pain	26 (13.4)
Oedema peripheral	26 (13.4)
Constipation	25 (12.9)
Stomatitis	23 (11.9)
Hypomagnesaemia	22 (11.3)
Insomnia	21 (10.8)
Cough	20 (10.3)

Source: TAK-981 IB Edition 5, Table 5.e (data cutoff date: 28 June 2022).
IB: investigator's brochure; TEAE: treatment-emergent adverse event.

In Study TAK-981-1002, the maximum tolerated dose (MTD) was determined to be 120 mg; the recommended Phase 2 dose (RP2D) for single agent TAK-981 is 90 mg given BIW (Days 1, 4, 8, and 11) in a 21-day cycle. Out of the 92 patients, 4 dose-limiting toxicities (DLTs) were reported in the single-agent study: transient Grade 3 serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations at 60 mg BIW, Grade 3 recurrent pneumonitis after a previous pneumonitis with an anti-PD-1 inhibitor at 90 mg BIW, and 2 at 120 mg BIW, transient Grade 3 stomatitis and transient Grade 3 cognitive disturbance with Grade 2 lethargy. The most common (≥20%) TEAEs in Study TAK-981-1002 across 10 dose levels (3-120 mg) and 3 dosing schedules (Days 1, 4, 8, and 11; Days 1 and 8; and Days 1, 8, and 15 in a 21-day cycle) were fatigue, nausea, headache, diarrhea, pyrexia, dyspnea, vomiting, and decreased appetite, anaemia, and dyspnoea. Reversible CRS was reported in 9 patients with 5 patients experiencing Grade 1 events (Grade 1 or 2 fever only) and 4 patients experiencing Grade 2 events (ie, fever and low peripheral oxygen saturation or low blood pressure). Grade 2 CRS was managed symptomatically (eg, oral antipyretics for fever, in addition to oxygen for hypoxia or

IV fluids for low blood pressure). No patient with CRS required vasoactive drug support or anti-IL-6 directed therapies.

Refer to the TAK-981 IB for additional details.

Overall, TAK-981 has been well tolerated. The majority of the observed adverse events (AEs) were consistent with the patients' underlying cancer disease.

4.3 Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G4 (IgG4) mAb with 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) (Keytruda (pembrolizumab) Injection for Intravenous Use 2023). 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 several indications (Keytruda (pembrolizumab) Injection for Intravenous Use 2023).

4.4 Rationale for the Proposed Study

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010). However, currently only a minority of patients respond to immunotherapeutics.

Combination strategies to help increase antigen release and T-cell priming, promote T-cell activation and homing, or improve the tumor microenvironment can help overcome the tumor immune-evasive mechanisms and maximize efficacy to ultimately benefit the majority of patients. Currently, interest on the cellular elements participating in the initiation of the tumor immunity cycle, has emerged as a key combination strategy to overcome intrinsic resistance to CPIs.

Triggering the release of modulators of the innate immune response such as Type I IFNs may activate DCs and induce pro-inflammatory cytokines and chemokines that lead to increased antigen cross presentation, T-cell activation and recruitment to the tumor sites, or the modulation of the TME. In addition, most of the antigen-presenting cells, tumor-associated macrophages, and NK cells in the TME are considered dysfunctional (Broz et al. 2014), which can lead to ineffective activation and recruitment of antitumor-specific T-cells and resistance to CPIs. Therefore, the induction of Type I IFN signal in cells of the innate immune response may be required to generate optimal DC activation, cross-priming and recruitment of CD8 T-cells, and to reinvigorate the adaptive immune response.

Preclinical evidence supports the above synergy. In the CT26 syngeneic tumor model, which did not show single agent responsiveness to either TAK-981 or an anti-mouse PD-1 antibody, combination treatment resulted in a significant survival benefit. Similar observations were noted in the MC38 tumor model in combination with anti-mouse CTLA4. Flow cytometry analysis revealed that those CT-26 tumors exhibiting marked growth inhibition in response to treatment

with the TAK-981 and anti-PD-1 combination showed enhanced activation of CD8+ T-cells compared to vehicle or single-agent treated tumors (sponsor data on file).

Therefore, the induction of a Type I IFN signal in the cells of the innate immune response in combination with the reinvigoration of the CD8 effector population with a CPI may translate into a significantly higher clinical benefit in a broader patient population than treatment with CPIs alone.

The pharmacodynamic studies performed to date at dose levels ranging from 3 to 120 mg provide evidence of dose-dependent target engagement (TAK-981-SUMO adduct) and SUMOylation pathway inhibition in blood and skin; induction of a Type I IFN response assessed by several complementary methods, including gene expression in blood and increase in plasma cytokines and chemokines; and activation of an innate and adaptive response observed by an increase in the proportion of CD69-positive NK and T-cytotoxic cells in the circulation, respectively. In total, the evidence for Type I IFN response is most convincing beginning at the 60 mg cohort and onwards.

4.5 Rationale for the Proposed Patient Population

The objective of this study is to determine the safety and tolerability of TAK-981 in combination with pembrolizumab, and whether the combination leads to a higher objective response rate than current treatment options in patients with select solid tumor types.

This is a multicenter, nonrandomized, multi-cohort study of TAK-981 in combination with pembrolizumab in patients with advanced solid tumors. Patients with any of the 4 specified solid tumor types (NSCLC, cervical, microsatellite stable colorectal cancer [MSS-CRC], cutaneous melanoma) will be enrolled. These tumor types were selected because (1) each represents a significant unmet medical need in the metastatic/refractory setting, (2) there is some evidence of limited clinical response to checkpoint blockade for these indications (Brahmer et al. 2015; Chung et al. 2019; Gadgeel et al. 2019; Gandhi et al. 2018; Herbst et al. 2016; Horn et al. 2017; Le et al. 2015; O'Neil et al. 2017; Overman et al. 2018; Overman et al. 2017; Reck et al. 2019; Rittmeyer et al. 2017; West et al. 2019), and (3) these indications broadly represent different immune contextures (inflamed, immune excluded, and immune desert). This approach will permit the assessment of the impact of TAK-981 on the tumor microenvironment of different tumors and the ability to induce and/or enhance an anti-tumor immune response.

4.5.1 Rationale for the Phase 2 Dose of TAK-981 in TAK-981-1502

Traditionally, the RP2D of cytotoxic anticancer agents was determined by DLTs given the assumption that the highest tolerable dose could result in better therapeutic activity. For some current drugs, such as TAK-981, with new mechanisms of action, the classical approach using only toxicity to define a RP2D may not be sufficient (Hansen et al. 2017). With targeted drugs, increasing doses beyond a certain level may not enhance the therapeutic activity, DLTs and a MTD may not be observed, and more serious TEAEs may only occur after multiple cycles of therapy (Shah et al. 2021). In addition to safety and tolerability, biological results, such as PK, pharmacodynamics, and efficacy, may also be useful in identifying a dose to evaluate in Phase 2

with these molecularly targeting agents, for which clinical benefit is not necessarily dose dependent. Therefore, the optimal method to define Phase 2 dose remains unclear in this setting (Shah et al. 2021) (Hansen et al. 2017).

As per protocol in Study TAK-981-1502, the dose to be evaluated in the Phase 2 expansion could be the MTD, based on observed DLTs following Bayesian logistic regression modeling guidance; alternatively, the expansion dose could be a dose below MTD considering other non-DLT safety and tolerability information as well as other data, including but not limited to PK, pharmacodynamic, and exposure/response findings. Further, the dose and schedule for the combination of TAK-981 and pembrolizumab to be taken forward for future efficacy studies could be determined either at the end of Phase 1 or Phase 2, considering all these circumstances. Overall, the Phase 2 dose will be determined from the collective experience in the clinic, considering the safety data, preliminary PK data, preliminary pharmacodynamics data, and any observed early antitumor activity.

In study TAK-981-1502, other parameters in addition to toxicity, such as PK, pharmacodynamics, and efficacy, were considered in the decision regarding the dose(s) to be evaluated in the Phase 2 expansion. Dose-dependent pharmacological effects, defined by target engagement and Type I IFN signaling, have been reported with similar magnitude and duration of pharmacodynamic responses when administered alone or in combination with pembrolizumab. These pharmacodynamic readouts were observed from the TAK-981 dose level of 60 mg and up to the dose level of 120 mg. Across the doses evaluated in this study, the PK of TAK-981 was linear with approximately dose-proportional increases in area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}). There was no accumulation of TAK-981 from C1D1 to C1D8 after either QW or BIW dosing, and plasma exposures were similar when TAK-981 was administered alone or in combination with pembrolizumab. PK/pharmacodynamics relationship modeling show dose-dependent target engagement that begins to plateau approximately at the 60 mg dose with a near maximal pharmacodynamic effect in terms of Type 1 IFN effector cell activation at the 120 mg dose of TAK-981. The currently available data in the dose- or exposure-response analyses have not been able to inform a dose selection, likely because of the small heterogenous sample sizes in some of the dose cohorts in this Phase 1 dose escalation phase. As previously noted, in this study combining TAK-981 with pembrolizumab, MTD was not identified, and antitumor activity has been seen across 90 BIW and 120 mg QW dose levels.

Therefore, considering the totality of the data from this study (TAK-981-1502) and factoring in safety, PK, and pharmacodynamics data from the FIH single-agent study (Study TAK-981-1002), upon implementation of Amendment 6, TAK-981 dose of 90 mg BIW will be evaluated in Phase 2 expansion Cohorts A to F, while the TAK-981 dose of 120 mg QW will be initially evaluated in Cohort A and F. Additional cohorts of TAK-981 at 120 mg QW may be opened in the protocol-specified cohorts to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

4.5.2 Rationale for the Tumor and Blood Tissues Collection

4.5.2.1 Tumor Biopsies

For patients in Phase 2, baseline (pretreatment) tumor collection is mandatory. Either a fresh tumor biopsy or banked tumor taken within 12 months of enrollment is required. This sample will be assessed for features of the tumor and/or tumor microenvironment including immune cell content and tumor mutations.

The collection of paired tumor biopsies at screening and on treatment will be encouraged (but optional) for all patients enrolled in the study. When provided, paired tumor biopsies will be used to determine TAK-981-SUMO adduct formation and SUMO pathway inhibition, as well as expressional and functional modulation of the immune response in the tumor/TME. Induction of an innate and/or adaptive immune response and checkpoint modulation in the tumor and TME will be assessed by measuring levels of IFN-regulated gene transcripts (messenger RNA) as well as by measuring levels of PD-1 and PD-L1 expression and activation state of tumor-infiltrating lymphocytes and myeloid cells, including NK cells and macrophages.

4.5.2.2 Blood

Blood samples will be collected to demonstrate TAK-981-SUMO adduct formation, SUMO pathway inhibition, and activation of an innate and/or adaptive immune response. This will be assessed by measuring levels of select plasma chemokines and cytokines (eg, CXCL10, MCP-1, and macrophage inflammatory protein MIP-1β), by detection of up-regulation of Type 1 IFN pathway-related genes, and by cellular markers of NK and T cell activation, T cell proliferation, and exhaustion. Plasma samples will be collected for evaluation of cell-free DNA (cfDNA) for assessment of tumor mutation burden.

4.6 Potential Risks and Benefits

TAK-981 is currently being evaluated as a single agent in the FIH study TAK-981-1002, in combination with rituximab in the Phase 1b/2 study TAK-981-1501, and in combination with anti-CD38 monoclonal antibodies in the Phase 1b/2 study TAK-981-1503, and, as such, the clinical benefits and risks have not yet been completely determined. The only serious adverse reaction considered expected for safety reporting purposes across the ongoing TAK-981 studies is pyrexia. Preliminary safety information in described in Section 4.2.6.

During this study, risk mitigation strategies include but are not limited to the following: strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and SAEs by the sponsor.

4.6.1 Potential Drug Interactions

TAK-981 is metabolized by cytochrome P-450 (CYP)2C9, 2C19, 2D6, 3A4, and aldehyde oxidase. CYP3A4/5 and aldehyde oxidase were the major contributors to the metabolism of TAK-981 with 70% to 76% and 19.1% contribution, respectively.

Pembrolizumab undergoes catabolism to small peptides and single amino acids via general protein degradation routes and does not rely on metabolism for clearance (Longoria and Tewari 2016).

Therefore, the potential risk for drug-drug interactions in patients treated with a combination of TAK-981 and pembrolizumab is very unlikely.

4.6.2 Potential Effects of TAK-981 Based on TAK-981 Nonclinical Studies

The potential risks listed below are based on findings from GLP repeat-dose nonclinical toxicology studies with QW or BIW dosing in rats and dogs, and a single-dose safety pharmacology study in dogs. These events may or may not develop in human patients treated with TAK-981.

Clinical study protocols for TAK-981 will include monitoring for the potential AEs specified for this compound using routine laboratory evaluations, urinalysis, cardiac monitoring, physical examinations, and disease assessment. The timing of these tests and evaluations is detailed in the schedule of events (SOE) (Appendix A). Additional tests and evaluations will be considered based on symptoms and findings observed in the study. It is possible that administration of TAK-981 will result in toxicities that were not observed or predicted from the completed nonclinical studies conducted in animals.

Further details for TAK-981 administration and safety event management can be found in the Guidance for Investigator section of the IB.

4.6.2.1 Lymphoid and Hematopoietic Effects

Dose-dependent reversible or partially reversible lymphoid/hematopoietic effects, including peripheral lymphopenia and decreased cellularity in lymph nodes, spleen, thymus, gut-associated lymphoid tissue, and bone marrow were observed in rats and dogs. Decreased cellularity of lymphoid tissues contributed to decreases in leukocyte counts. These findings could be associated with increased susceptibility to certain forms of infection that were not observed in GLP toxicology studies.

Lymphopenia may predispose patients to certain forms of infection that were not observed in the GLP-compliant toxicology studies. Prolonged lymphopenia and CD4 counts below 200/µL have been associated with opportunistic infections. Prophylaxis for pneumocystis pneumonia or herpes zoster is not required; however, in cases of prolonged lymphopenia, or in patients with a previous history of shingles, it might be initiated per standard of care.

As of the data cutoff for the IB Edition 5 in the ongoing clinical studies (N = 194), instances of lymphocyte count decreased (6.2%) related to TAK-981 have been reported. No serious infections or opportunistic infections associated with lymphocyte count decrease have been reported to date. Herpes simplex viral infections have been observed (2.6% related to TAK-981) and were self-limited, resolving within 14 days.

In this study, absolute lymphocyte counts will be monitored, and subpopulations will be assessed regularly, especially CD4 and CD8 counts. A prolonged CD4 count below 200/µL (National

Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) is the strongest predictor for opportunistic infections. The initiation of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and herpes virus prophylaxis will be considered at the discretion of the investigator.

4.6.2.2 Effects in Renal Pelvis

TAK-981–related effects were observed in the kidney in dogs following repeat daily to BIW dosing at higher doses and consisted of inflammation and arteriolar fibrinoid necrosis localized to the renal pelvis. There were no effects in the renal cortex or medulla; there were no repercussions on kidney function or conventional urinary test parameters. After a 10-day nondosing period, arteriolar fibrinoid necrosis was completely reversed and inflammation was partially reversed. Lesions in the renal pelvis could be associated with alterations in urinary sediment and susceptibility to urinary infections in the clinic, although these potential effects were not observed in dogs.

Inflammation in the renal pelvis suggests a local effect of concentrated drug or a metabolite. Patients will be asked to maintain adequate hydration (1.5 to 2 L/day) 48 hours before initiating therapy, and IV fluid administration on Cycle 1, Day 1 (C1D1) will be recommended for those who cannot maintain adequate oral hydration. Patients will be monitored for renal function, and in patients with significant alterations in urinalysis, urine sediment analysis will be required.

4.6.2.3 IRRs and Potential for CRS

The mechanism of action of TAK-981 involves Type I IFN signaling. Thus, the potential for IRRs and CRS was examined in the twice-weekly GLP toxicity studies in rats and dogs. Modest increases in MCP-1, IP-10 (rats only), and RANTES (rats only) were observed while no increases in cytokines related to CRS were observed.

An in vitro cytokine release assay was performed with human whole blood for hazard identification of clinically significant CRS. There were no effects on cytokines typically associated with CRS; TAK-981-related effects were limited to moderate increases in IP-10 at ≥0.5 µM.

In a single-dose safety pharmacology study, acute and transient mild increases in body temperature and reactive increases in heart rate without changes in blood pressure were observed in dogs from 6 to 24 hours after the infusion. In a single-dose non-GLP-compliant dog toxicity study, fever was considered a DLT at the high dose of 12 mg/kg. Non-dose-limiting increases in body temperatures were noted in studies with daily and once weekly dosing at ≥3 mg/kg. No changes in body temperature, heart rate, or respiratory rate were observed in the GLP-compliant twice-weekly dog study. CCI

As a precaution for IRRs/CRS, patients in dose escalation will be monitored for a minimum of 6 hours after the first infusion of TAK-981. For the remaining infusions during Cycle 1 (and only

in case no IRR AEs are being observed), the patient will be observed a minimum of 2 hours after the end of infusion of the last study drug and can only be discharged if clinically stable.

As an additional precaution measure, for the first cohort in dose escalation only, 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. Subsequent cohorts will not require staggering between patients.

4.6.2.4 Injection Site Reactions

The local irritancy potential of TAK-981 was evaluated at the IV administration site in the GLP-compliant repeat-dose toxicity studies in rats and dogs. Effects at the injection site, including potentiation of procedure-related subcutaneous hemorrhage, inflammation, and necrosis, were observed in rats only. The shorter needle length and frequent movement of conscious rats likely resulted in extravasation. Of note, TAK-981 is a solution with low pH that should be diluted, as defined in the pharmacy manual.

Sites will be informed to enforce careful observation of the infusion site in case a peripheral vein is used for administration. In general, infusion through a central line or subcutaneous reservoir is preferred for TAK-981 administration.

4.6.2.5 Reproductive and Development Toxicity

Reproductive and developmental toxicity studies have not yet been conducted. Therefore, the effects of TAK-981 on fertility and the developing fetus are not known at this time. Reproductive tissues were weighed and examined microscopically as part of the GLP-compliant repeat-dose toxicity studies with QW or BIW dosing in sexually mature rats and dogs. TAK-981–related reproductive findings were not observed in the rat and dog with BIW dosing and in the dog study with QW dosing. However, in the rat study with QW dosing at ≥20 mg/kg, there was reversible single cell necrosis in multiple male and female reproductive tissues, inflammation in the prostate gland, and (at ≥5 mg/kg) partially reversible acinar cell trophy in the male mammary gland. Additionally, in a non–GLP-compliant 7-day repeat dose toxicity study in male rats, TAK-981–related effects were noted in multiple reproductive tissues in animals that also had significant systemic toxicity, including minimal to mild single cell necrosis of the epithelium (≥10 mg/kg), and at 40 mg/kg minimal to mild atrophy, karyomegaly, increased mitotic figures, and/or degeneration/necrosis.

Therefore, female patients and female partners of male patients participating in this study should avoid becoming pregnant. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below:

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR

- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

4.6.2.6 Genotoxicity

TAK-981 was not mutagenic in an in vitro bacterial mutagenesis Ames assay. However, in an in vivo rat bone marrow micronucleus assay, TAK-981 increased induction of micronuclei and was therefore considered to be positive for in vivo genotoxicity at ≥5 mg/kg. TAK-981 was considered clastogenic in an in vitro chromosomal aberration test using human peripheral blood lymphocytes. In compliance with International Council for Harmonisation (ICH) S9 guidance (2009), carcinogenicity assessment is not planned.

The potential effects listed above are based on toxicology findings in the nonclinical studies with TAK-981; they may or may not present with similar severity in humans. It is possible that administration of TAK-981 will result in toxicities that were not observed or predicted from the completed nonclinical studies conducted in animals.

4.6.3 Potential Effects of TAK-981 Based on TAK-981 Clinical Studies

The safety of TAK-981 as single agent has been evaluated in patients with solid tumors or lymphomas in the FIH clinical Study TAK-981-1002, in combination with rituximab in patients with lymphomas in the clinical Study TAK-981-1501, in combination with pembrolizumab in patients with select solid tumor types in Study TAK-981-1502, and in combination with anti-CD38 mAbs in patients with relapsed and/or refractory multiple myeloma in Study TAK-981-1503 (Section 4.2.6). Refer to current IB for more details.

4.6.4 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 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 FDA-approved package insert (Keytruda (pembrolizumab) Injection for Intravenous Use 2023).

4.6.5 Potential Overlapping Toxicities

Nonclinical toxicology studies evaluating the combination of TAK-981 and pembrolizumab were not conducted and are not warranted per ICH S9 (2009). Pembrolizumab is a mAb that binds to the human PD-1 receptor and blocks the interaction of PD-1 with PD-L1/PD-L2.

Compared to treatment with TAK-981 alone, synergistic toxicity as assessed by increased mortality or more significant decreases in body weight was not observed in mouse tumor-bearing models administered TAK-981 in combination with an antimurine PD-1 antibody. TAK-981 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 TAK-981. Details regarding the full safety profile of pembrolizumab can be found in the FDA approved package insert (Keytruda (pembrolizumab) Injection for Intravenous Use 2023).

To minimize the risk to patients treated with TAK-981 and pembrolizumab, the proposed starting dose for TAK-981, in combination with pembrolizumab, will be at least 1 dose level below the clinically tested highest safe dose defined in the single-agent FIH study (Study TAK-981-1002) and will be determined by the sponsor and participating investigators after review of the emerging safety data from the ongoing FIH single-agent study. Pembrolizumab will be administered at the approved dose and schedule of 200 mg IV once every 3 weeks to maximize the possibility of observing clinical benefit.

4.6.6 Coronavirus Disease 2019 Pandemic

The coronavirus disease 2019 (COVID-19) pandemic has affected health care and specifically cancer care broadly across the globe. Based on current knowledge, the benefit/risk assessment for patient participation in this study remains favorable. The benefit/risk considerations for patient participation should be evaluated by the investigator on a patient-by-patient basis taking into consideration the current local situation, guidelines, and recommendations. Investigators should follow local recommendations and guidelines with regards to COVID-19 precautions, vaccination, and treatment.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

Phase 1b:

- To determine the safety and tolerability of TAK-981 in combination with pembrolizumab in patients with select solid tumor indications.
- To establish the recommended Phase 2 dose (RP2D).

Phase 2:

- To evaluate the preliminary efficacy of TAK-981 at the RP2D in combination with pembrolizumab in patients with select solid tumor indications.

5.1.2 Secondary Objectives

The secondary objectives are:

Phase 1b:

- To characterize the PK of TAK-981 in combination with pembrolizumab.
- To determine the MTD and/or pharmacologically active dose (PAD) of TAK-981 when administered in combination with pembrolizumab.
- To assess the preliminary antitumor activity of TAK-981-pembrolizumab combination.
- To assess target engagement of TAK-981 (SUMO-TAK-981 adduct formation) and SUMOylation pathway inhibition in blood.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with pembrolizumab in select solid tumors as measured by disease control rate (DCR), durable response rate (DRR), DOR, time to response (TTR), time to progression (TTP), PFS, and OS.
- To evaluate the safety and tolerability of TAK-981 in combination with pembrolizumab.
- To collect PK data to contribute to population PK and exposure-response (safety/efficacy) analysis.

5.1.3 Exploratory Objectives

The exploratory objectives are:

- To assess pharmacodynamic biomarkers in peripheral blood such as immune cell activation and gene and protein expression.

- To assess pharmacodynamic biomarkers in tumors such as SUMO pathway inhibition, gene expression and tumor-infiltrating immune cells.
- To explore potential predictive biomarkers of response to combination therapy by exploring correlations between baseline molecular and cellular characterization of peripheral blood and tumor biomarkers (this may include genomic/transcriptomic/proteomic approaches) with efficacy and other clinical endpoints of interest.
- To explore mechanisms of resistance in peripheral blood samples collected from patients who initially respond to TAK-981 in combination with pembrolizumab therapy and then exhibit disease progression.
- Exploratory endpoints, such as evaluating circulating serum proteins, cell-free DNA (cfDNA), exosomes, and mRNA signatures associated with response or resistance to TAK-981 in combination with pembrolizumab treatment, will be executed as warranted to further understand TAK-981 mechanism of action and potential responsive patient populations.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

Phase 1b:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0, except CRS that will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS.
- Occurrence of DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- ORR (CR + PR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST, Version 1.1).

5.2.2 Secondary Endpoints

The secondary endpoints are:

Phase 1b:

- ORR, DCR, DRR, DOR, TTR, TTP, and PFS as assessed by the investigator according to RECIST, Version 1.1 and the RECIST consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials (iRECIST).
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood.
- TAK-981 plasma concentration-time data.

Phase 2:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0, except CRS that will be graded according to ASTCT Consensus Grading for CRS.
- DCR, DRR, DOR, TTR, TTP, PFS, and OS as assessed by the investigator according to RECIST, Version 1.1 and iRECIST; ORR as assessed by the investigator according to iRECIST.

5.2.3 Exploratory Endpoints

The exploratory endpoints are:

- TAK-981-SUMO adduct formation and SUMO pathway inhibition in tumor tissue.
- Changes in pharmacodynamic biomarkers in peripheral blood such as immune cell activation and gene and protein expression.
- Changes in pharmacodynamic biomarkers in tumors such as gene expression and tumor-infiltrating immune cells.
- Correlative studies to explore predictive biomarkers of response to combination therapy.
- Correlative studies to explore mechanisms of resistance to combination therapy.
- Exploratory endpoints such as evaluating circulating serum proteins, cfDNA, and mRNA signatures associated with response or resistance to TAK-981 in combination with pembrolizumab treatment will be executed as warranted.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The study consists of 2 phases:

- Phase 1b: Dose escalation.
- Phase 2: Expansion in select indications.

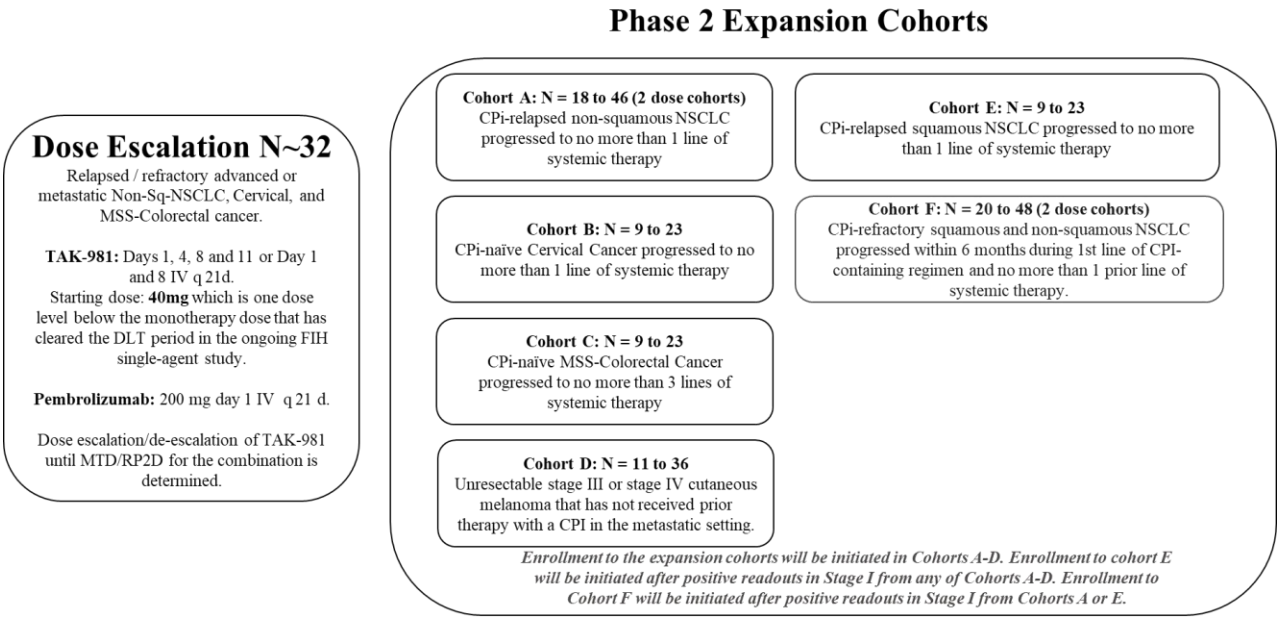
The study will consist of a screening period (Day –28 to −1), a treatment period, an end of treatment (EOT) visit, and 2 follow-up visits at 30 and 90 days after the last dose occurring when treatment is discontinued for any reason, and a survival follow-up period lasting for a maximum of 12 months for each patient after their last dose of study drug to monitor disease and survival status. Day 1 of the study (baseline) will be defined as the first day a patient receives TAK-981. One cycle of treatment will be defined as 21 days. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will receive treatment with TAK-981 and pembrolizumab for up to 24 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the study or study drugs occurs. Treatment may be continued beyond disease progression, with

sponsor approval, if, in the opinion of the investigator, the patient continues to experience clinical benefit.

A study design scheme is provided in Figure 6.a.

Figure 6.a TAK-981-1502 Study Design



CPI: checkpoint inhibitor; DLT: dose-limiting toxicity; FIH: first in human; IV: intravenous; MSS: microsatellite stable; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein 1 ligand; q21d: every 21 days; RP2D: recommended Phase 2 dose.

6.2 Phase 1b–Dose Escalation

The Phase 1b portion of the study is a dose escalation of TAK-981 in combination with pembrolizumab at a fixed dose in patients with nonsquamous NSCLC, cervical cancer, or MSS-CRC. Dose escalation of TAK-981 will be guided by a Bayesian Optimal Interval Design (BOIN) to guide the RP2D for the combination therapy. The RP2D will be determined from the collective experience in the clinic considering the safety data including the pattern of irAEs across all patients beyond the DLT window, preliminary PK data, preliminary pharmacodynamic data, preliminary translational data, and any early antitumor activity observed along with the decision boundaries from the BOIN design.

In the first cohort, patient enrollment will be staggered between the first and second patients by 7 days during dose escalation. 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 will not require staggering between patients.

A safety monitoring committee (SMC) composed of the principal investigators, and sponsor clinician will regularly review safety data to ensure patients' safety throughout the Phase 1b portion of the study and make decisions on dose escalation.

Circumstances that may warrant enrollment hold include: any death or ≥ 2 Grade 4 events not clearly related to underlying disease, progression of disease, or intercurrent illness, and at least possibly related to the investigational product.

The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients. The decision to halt treatment of ongoing patients, resume enrollment, terminate the study, or amend the protocol will be made only after a full review of the safety data by the SMC and the safety management team.

6.3 Phase 2–Expansion in Select Indications

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with pembrolizumab in patients with select cancers. The following cohorts will be enrolled:

- Cohort A: Non-squamous NSCLC.
- Cohort B: Cervical cancer.
- Cohort C: MSS-CRC.
- Cohort D: Cutaneous melanoma.
- Cohort E: Squamous NSCLC.
- Cohort F: CPI refractory squamous or nonsquamous NSCLC.

Enrollment will be initiated in Cohorts A through D. Enrollment to Cohort E will be initiated after positive readouts in Stage 1 from any of Cohorts A through D. Enrollment to Cohort F will be initiated after positive readouts in Stage 1 from any of the lung cancer cohorts (Cohorts A or E).

Cohorts A to E will be assessed separately using an adaptive 2-stage design for a single proportion. For Stage 1, each cohort will be analyzed when a prespecified number of patients (as defined in Section 13.0) have been enrolled and had the potential to have at least 1 post-treatment scan (ie, after the first disease assessment, 2 months from C1D1). Enrollment will be paused at the end of Stage 1 for each arm. If the prespecified minimal response rate is not achieved in the first stage for a given cohort, that cohort will be closed to enrollment. If the required response rate during Stage 1 is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients for that cohort has been reached (as defined in Section 13.0). The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have had the opportunity to complete the 6-month disease assessment.

The preliminary safety and efficacy of TAK-981 in combination with pembrolizumab in primary refractory NSCLC will be assessed in Cohort F, which includes 2 dose-expansion levels

following Simon's 2-stage design. For Stage 1, each cohort will be analyzed when a prespecified number of patients (as defined in Section 13.0) have been enrolled and had the potential to have at least 1 posttreatment scan (ie, after the first disease assessment, 2 months from C1D1). However, in the absence of significant safety signals and conditional to passing the futility analysis in Cohorts A or E, enrollment to Cohort F may continue (up to 15 subjects in each dose level) after the completion of enrollment of Stage1 patients and before response evaluation of these patients. Cohorts A, E, and F are independent study cohorts and will be separately evaluated for efficacy.

In Phase 2, TAK-981 will be evaluated using 2 dose regimens:

- A dose of 90 mg BIW (a lower biologically active dose; BIW will be on Days 1, 4, 8, and 11) during the first 3 cycles followed by 90 mg QW (on Days 1 and 8), both in combination with a fixed dose of pembrolizumab.
- A dose regimen of 120 mg QW (Days 1 and 8) in a 21-day cycle (the highest, safe dose level studied in Phase 1, but with exposures below the MTD in the first-in-human Phase 1 study of TAK-981 [120 mg BIW] as a single agent) in combination with a fixed dose of pembrolizumab in patients with NSCLC.

The safety and preliminary efficacy of TAK-981 120 mg QW will be evaluated in a lead-in safety cohort that will initially enroll 6 patients with an enrollment pause until the 6 patients have had the opportunity to complete the first 3 cycles (Cohort A). Enrollment in the 120 mg cohort of nonsquamous non-small cell lung cancer will be discontinued if ≥4 out of 6 treated patients require dose reduction or drug withdrawals due to TAK-981–related AEs within the first 3 cycles. If dose reduction or drug withdrawals due to TAK-981–related AEs within the first 3 cycles are observed in ≤3 out of 6 treated patients, enrollment will be expanded to 9 response-evaluable patients to complete Stage 1. Should the 120 mg dose be considered safe in nonsquamous-NSCLC, additional cohorts of TAK-981 at 120 mg on Days 1 and 8 in combination with pembrolizumab may be opened in the protocol-defined cohorts without the need for an enrollment pause after the first 6 patients.

For all cohorts, the criteria to proceed to Stage 2 are provided in Section 6.3.1.

During Phase 2, patients will be concurrently enrolled, and the sponsor/designee will assign patients to a respective cohort and, for Cohort A and F only, to a respective TAK-981 dose group (120 mg QW or 90 mg BIW). During Phase 2, an independent data monitoring committee (IDMC) will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

6.3.1 Early Stopping Rules

In the Phase 2 portion of the study, Grade 4 or higher drug-related AEs will be monitored. For Cohorts A to C, and E, starting from the first 9 response-evaluable patients and then every

4 response-evaluable patients up to the approximate maximum number of 24 patients, accrual to the study will be suspended if:

- Grade 4 drug-related AEs meet the stopping bounds of the number of ≥3/9, ≥4/13, ≥5/17, ≥6/21, ≥6/24; or
- At any time if 1 or more patients present with fatal drug-related AEs.

For Cohort D, starting from the first 11 response-evaluable patients and then every 4 response evaluable patients up to the approximate maximum number of patients 36, accrual to the study will be suspended if:

- Grade 4 drug-related AEs meet the stopping bounds of the number of ≥4/11, ≥4/15, ≥5/19, ≥6/23, ≥7/27, ≥7/31, ≥8/35, ≥8/36; or
- At any time if 1 or more patients present with fatal drug-related AEs.

For Cohort F, starting from the first 10 response-evaluable patients and then every 4 response-evaluable patients up to the approximate maximum number of patients 24, accrual to the study will be suspended if:

- Grade 4 drug-related AEs meet the stopping bounds of the number of ≥3/10, ≥4/14, ≥5/18, ≥6/22, ≥6/24; or
- At any time if 1 or more patients present with fatal drug-related AEs.

After review and consideration by the IDMC, a decision will be made as to whether accrual can be resumed.

The stopping bounds for Grade 4 drug-related AEs are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rule is met, there is 80% probability that the true toxicity rate is greater than 16% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate (Thall and Sung 1998).

6.4 Number of Patients

A total of approximately 231 patients will be enrolled in this study: approximately 32 patients in the Phase 1b dose escalation and approximately 76 to 199 patients in the Phase 2 portion of the study (approximately 9-23 patients for Cohorts A-C, and E, approximately 11-36 patients for Cohort D, and approximately 10-24 for Cohort F).

6.5 Patient Replacement

In the Phase 1b part of the study, patients who are considered to not be evaluable for DLT assessment (as defined in Section 8.3) will be replaced.

6.6 Duration of Study

The expected duration for this study is 48 months: approximately 24 months for enrollment and approximately 24 months for treatment and/or follow-up.

6.6.1 Duration of an Individual Patient's Study Participation

Patient participation will include screening, treatment, and follow-up. Screening will last up to 28 days before the first dose of study drug, during which the patient's eligibility and baseline characteristics will be determined. Treatment with TAK-981 and pembrolizumab will be administered for up to 24 months or until patients meet any of the discontinuation criteria in Section 8.5.4. Patients who have completed treatment or have discontinued treatment will be followed for survival for up to 12 months.

6.6.2 End of Study/Study Completion Definition and Planned Reporting

The end of study will occur when all patients have had the opportunity to complete 24 months of treatment; have been followed for survival for a minimum of 12 months after the last patient has been discontinued or completes treatment; until all patients have died, withdrawn consent, or are lost to follow-up; or the study is terminated (whichever occurs first).

6.6.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary (Phase 1):		
Frequency of TEAEs overall and per DL	Standard safety assessments	Up to 48 months
Number of patients with DLTs per DL	Standard safety assessments	Up to 48 months
Number/percentage of patients with Grade ≥3 TEAEs	Standard safety assessments	Up to 48 months
Number/percentage of patients with 1 or more SAEs	Standard safety assessments	Up to 48 months
Number/percentage of patients with 1 or more TEAEs leading to dose modifications (delay, interruption, or reduction) and treatment discontinuations	Standard safety assessments	Up to 48 months
Number/percentage of patients with clinically significant laboratory values	Standard safety assessments	Up to 48 months
Primary (Phase 2):		
ORR as assessed by the investigator according to RECIST, Version 1.1	Standard efficacy assessments	Up to 60 months
Secondary:		
Data permitting, PK parameters after the dose administration of TAK-981 on C1D1 and C1D8: C_{max}, t_{max}, AUC_t, AUC_∞, $t_{1/2z}$, CL, V_{ss}	Standard PK parameters to allow determination of PK profile	Up to 60 months
ORR as defined by the investigator according to iRECIST modification.	ORR	Up to 60 months
DCR	DCR	Up to 60 months

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
DRR	DRR	Up to 60 months
DOR	DOR	Up to 60 months
PFS	PFS	Up to 60 months
TTR	TTR	Up to 60 months
TTP	TTP	Up to 60 months
OS	OS	Up to 60 months
TAK-981-SUMO adduct formation and SUMO pathway inhibition	TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood	Up to 48 months

AUC_t: area under the plasma/blood/serum concentration-time curve from time 0 to time $_t$; AUC_∞: area under the plasma concentration-time curve from time 0 to infinity; CxDx; Cycle x, Day x; CL: total clearance after intravenous administration; C_{max}: maximum observed plasma concentration; DCR: disease control rate; DL: dose level; DLT: dose limiting toxicity; DOR: duration of response; DRR: durable response rate; iRECIST: consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SUMO: small ubiquitin-like modifier; TEAE: treatment-emergent adverse event; $t_{1/2z}$: terminal disposition phase half-life; t_{max}: time of first occurrence of C_{max}; TTP: time to progression; TTR: time to response; V_{ss}: volume of distribution at steady state after intravenous administration.

6.6.4 Total Study Duration

It is anticipated that this study will last for approximately 60 months.

6.6.5 Posttrial Access

Treatment with TAK-981 and/or pembrolizumab will be administered for up to 24 months. Patients that have completed the protocol defined course of therapy will no longer receive treatment administration and will be followed for survival as defined in Section 6.6.1.

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 male or female patients aged 18 years or older.
2. Be willing and able to provide written informed consent for the study.

3. Have a histologically or cytologically documented, advanced (metastatic and/or unresectable) cancer as listed below that is incurable:

   Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line standard of care treatment unless such treatments were completed less than 12 months prior to the current tumor recurrence.

   A. Non-squamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed and that has progressed on no more than 1 prior systemic therapy. In Phase 2, patients with nonsquamous NSCLC must have not received more than 1 prior systemic therapy and must not have presented with disease progression during the first 6 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy.

      Note: In Phase 1, patients with nonsquamous NSCLC and known driver mutations/genomic aberrations (eg, *EGFR*, B-Raf proto-oncogene mutation V600E [*BRAF* V600E], and ROS proto-oncogene 1 [*ROS1*] sensitizing mutations, neurotrophic receptor tyrosine kinase [*NRTK*] gene fusions, and *ALK* rearrangements) must have also shown progressive disease after treatment with a commercially available targeted therapy. In Phase 2, patients with driver mutations are not eligible.

   B. CPI-naïve cervical cancer (squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix) patients for whom prior standard first-line treatment has failed and who have received no more than 1 prior systemic line of therapy for recurrent or Stage IVB cervical cancer.

      Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric-type adenocarcinoma, clear-cell carcinoma, and mesonephric carcinoma. Histologic confirmation of the original primary tumor is required via pathology report.

      Note: First-line treatment must have consisted of platinum-containing doublet. Chemotherapy administered concurrently with primary radiation (eg, weekly cisplatin) is not counted as a systemic chemotherapy regimen.

   C. CPI-naïve MSS-CRC patients for whom prior standard first-line treatment has failed and who have progressed on/after no more than 3 chemotherapy regimens/lines.

      Note: Patients must have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens if indicated.

   D. Unresectable Stage III or Stage IV cutaneous melanoma that has not received prior therapy in the metastatic setting.

      Note: Patients with acral melanoma are not eligible. Patients who have presented with disease relapse after ≥6 months of the last dose of CPI or BRAF-MEK inhibitor in the adjuvant setting are eligible.

E. Squamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed. Patients must have not received more than 1 prior systemic therapy and must not have presented with disease progression during the first 6 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy.

F. Squamous or nonsquamous NSCLC for which prior standard first-line treatment containing an anti-PD-(1/L1) checkpoint inhibitor alone or in combination has failed within 6 months from the initiation of the CPI. Patients must not have received more than 1 prior systemic therapy in the metastatic setting.

Note: patients with driver mutations are not eligible.

4. Have at least 1 radiologically measurable lesion based on RECIST, Version 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
5. Patients in Phase 2 expansion cohorts must have a PD-L1 result in tumor tissue obtained from an FDA-approved, or Conformité Européene (CE)-marked, or locally equivalent PD-L1 test.
6. Willing to consent to mandatory pretreatment fresh tumor biopsy for Phase 2.

   Note: Pretreatment fresh tumor biopsy at screening can be replaced by a recent (≤12 months old) formalin-fixed, paraffin-embedded tumor specimen. For fresh tumor biopsies, the lesion must be accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal space, or those obtained with endoscopic procedures beyond the stomach or bowel).
7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
8. Demonstrate adequate organ function as described below:
   A. Platelet count $\geq 75.0 \times 10^9$/L.
   B. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.
   C. Hemoglobin ≥85 g/L (red blood cell [RBC] transfusion allowed ≥14 days before assessment).
   D. Calculated creatinine clearance ≥30 mL/min using the Cockcroft-Gault formula.
   E. Aspartate aminotransferase (AST, GOT) and alanine aminotransferase (ALT, GPT) ≤3.0 times the upper limit of normal (ULN), <5.0 times the ULN if liver enzyme elevations are due to liver metastases; bilirubin ≤1.5 times the ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 times the ULN, per discussion between the investigator and the medical monitor.
9. Left ventricular ejection fraction (LVEF) ≥40%; as measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan.

10. Have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.

    Note: Neuropathy Grade ≤2, any grade alopecia, or autoimmune endocrinopathies with stable replacement therapy are permitted.

11. Women of childbearing potential must have a negative serum/urine pregnancy test within 72 hours prior to receiving the first dose of study medication.

12. Female patients must meet 1 of the following:

    A. Postmenopausal for at least 1 year before the screening visit, or

    B. Surgically sterile, or

    C. If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 6 months after the last dose of study, or

    D. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

13. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

    A. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or

    B. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

14. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

7.2 Exclusion Criteria

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

1. Received treatment with systemic anticancer treatments or investigational products within 14 days before the first dose of study drug or 5 half-lives, whichever is shorter.

   Note: Low-dose steroids (oral prednisone or equivalent ≤10 mg per day), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed.

2. History of uncontrolled brain metastasis (evidence of progression by imaging over a period of 4 weeks and/or neurologic symptoms that have not returned to baseline). Patients with treated brain metastases are allowed provided they are radiologically stable, without evidence of progression for at least 4 weeks by repeat imaging, clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. Note: For asymptomatic patients, screening brain imaging is not required.
3. Second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy.
4. Major surgery ≤14 days from the first dose of study drug and not recovered fully from any complications from surgery.
5. Prior treatment with TAK-981.
6. Hypersensitivity to TAK-981, pembrolizumab, or any component of the drug product.
7. Baseline prolongation of the QT interval corrected using Fridericia's formula (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
8. History of immune-related AEs related to treatment with immune CPIs that required treatment discontinuation.
9. Receiving or requires the continued use of medications that are known to be strong or moderate inhibitors and inducers of CYP3A4/5 and strong P-glycoprotein (Pgp) inhibitors. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and Pgp inhibitors) before receiving a dose of TAK-981.
10. Receipt of any live vaccine within 4 weeks of initiation of study treatment.
11. History of autoimmune disease requiring systemic immunosuppressive therapy with daily doses of prednisone >10 mg/day or equivalent doses, or any other form of immunosuppressive therapy. Hormone replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for thyroid, adrenal or pituitary insufficiency) for endocrinopathies are not considered prohibited forms of systemic treatment of an autoimmune disease.
12. History of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
13. Has evidence of active, noninfectious pneumonitis.
14. History of allogeneic tissue or solid organ transplant.
15. Has active infection requiring systemic therapy.
16. Known history of HIV infection or any other relevant congenital or acquired immunodeficiency.

17. Known hepatitis B virus surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
18. History of any of the following ≤6 months before first dose: congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, uncontrolled hypertension despite appropriate medical therapy, ongoing symptomatic cardiac arrhythmias >Grade 2, pulmonary embolism or symptomatic cerebrovascular events, or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). Chronic atrial fibrillation on stable anticoagulant therapy is allowed.
19. 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.
20. Female patients who are pregnant or lactating and breastfeeding.

8.0 STUDY DRUG

Patients enrolled in the study will receive TAK-981 in combination with pembrolizumab.

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). All patients will receive TAK-981 and pembrolizumab as specified in the SOE (Appendix A).

Two treatment schedules will be evaluated. Each 21-day treatment cycle will consist of TAK-981 administration on Days 1, 4, 8, and 11 or Days 1 and 8. Alternative TAK-981 dosing schedules (eg, Day 1, or Days 1, 8, and 15 in 21-day cycles) may be permissible only after discussions between the sponsor and the investigators. The TAK-981 starting dose in the less dense schedule must not be higher than the dose level being tested in the Days 1, 4, 8, and 11 dosing schedule. Also, in patients with maximal clinical benefit, the TAK-981 dosing schedule can be changed after 6 months of therapy to a less frequent schedule after discussion with the sponsor.

Pembrolizumab will be dosed at the clinically approved dose of 200 mg on Day 1 of a 21-day cycle.

TAK-981 will be administered before pembrolizumab on days on which both TAK-981 and pembrolizumab are given on the same visit day. 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.

8.1.1 TAK-981

TAK-981 Injection (Solution for Infusion) is supplied in a single use vial containing 100 mg of TAK-981 sterile solution. TAK-981 is stored frozen at -25˚C to -15˚C. For specific information about the storage and handling of TAK-981 drug product, refer to the Pharmacy Manual.

TAK-981 must be thawed then diluted in 5% Dextrose or 0.9% Saline prior to use. TAK-981 vials and prepared dilutions should be protected from light. The prepared dilution must be administered within 4 hours if stored at ambient temperature, or within 24 hours if stored at 2˚C to 8˚C. Detailed thawing and dosage preparation instructions are provided in the Directions for Use located in the Pharmacy Manual. The diluted product will be administered by IV infusion over 1 hour. After the end of the infusion the IV line should be flushed accordingly to local standards.

The TAK-981 dose for each dose level in Phase 1b and for Phase 2 will be decided by the SMC composed of the principal investigators, and sponsor clinician at each end-of-cohort meeting. TAK-981 will be administered as a 60 ±10-minute IV infusion. If infusion reactions are observed, the length of the infusion can be extended up to 2 hours for all patients without requiring a protocol amendment.

During dose escalation, all patients at a given dose level will be monitored for C1D1 for drug administration and observation for a minimum of 6 hours after the end of infusion of TAK-981.

Patients can be discharged after the 6-hour observation period only if there are no signs and symptoms of acute toxicity like fever or significant changes in blood pressure and/or heart rate. Patients who experience any treatment-related AEs during the 6-hour observation period should be further monitored as clinically indicated. If no infusion reaction is observed on C1D1, subsequent monitoring for that patient during Cycle 1 can be reduced to 2 hours after the end of infusion of the last study drug.

In Phase 2, patients can be discharged after 1-hour observation if there are no signs of acute toxicity after the end of infusion of the last study drug.

Patients will be asked to maintain adequate hydration (1.5-2 L/day) 48 hours before initiating therapy and during C1D1, and IV fluid administration on C1D1 is recommended for those who cannot maintain adequate oral hydration.

Note: Fever is a common TEAE associated with the TAK-981 administration. Consider prescribing postinfusion antipyretic medications for up to 24 hours after the end of the TAK-981 infusion as a preventative measure. For any patient that has an infusion-related fever, consider prophylaxis with an antipyretic medication. Investigator may consider reducing, even discontinuing, predose and postdose antipyretics if the patient experiences no major infusion-related fever. The clinical site is responsible for sourcing any pre- and postmedications outlined in the protocol.

8.1.2 Pembrolizumab

Pembrolizumab is available as single-use vials of 50 or 100 mg of drug substance (Keytruda (pembrolizumab) Injection for Intravenous Use 2023).

The approved dose of pembrolizumab is 200 mg every 3 weeks (21-day cycle). Dose escalations or dose reductions of pembrolizumab are not allowed in this study. Pembrolizumab will be administered as a 30 ±10-minute IV infusion.

8.1.3 Additional Instructions for Treatment Administration

Vital signs will be monitored throughout study drug administration according to the SOE (Appendix A). All patients will be monitored for at least 2 hours after the end of infusion of the last study drug. After the administration of TAK-981 or pembrolizumab, the patient should be considered clinically stable by the investigator or designee before the next study drug is administered or the patient is discharged. From Cycle 2 onwards, if no infusion reaction is observed in the first cycle, post-infusion monitoring may not be required and the patient can be discharged from the site per investigator discretion.

In all cases, the administration of TAK-981 or pembrolizumab should occur in an area with access to resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Treatment must be stopped if the patient experiences symptoms compatible with an infusion reaction of Grade 2 or greater. The management of infusion reactions and CRS is detailed in Section 8.9.6 and Section 8.9.7, respectively.

Dose administration of TAK-981 and pembrolizumab should be performed on schedule; however, a dose delay of up to 3 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor (see Section 8.7). For patients in the DLT-evaluation period (Cycle 1) rescheduling is allowed for a maximum of 1 dose. At least 3 days should elapse between consecutive doses of TAK-981. On days on which both TAK-981 and pembrolizumab are administered, should the treatment day be rescheduled, both TAK-981 and pembrolizumab doses will be rescheduled.

As with other potentially toxic compounds, caution should be exercised in handling this drug. The use of gloves is recommended. Following topical exposure, events could include redness or blistering. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Administration through a central port is always preferred versus a peripheral line.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0 (NCI 2017), except CRS that will be graded according to ASCST Consensus Grading for CRS (Lee et al. 2019). In Phase 1b, DLT will be defined as any of the following events occurring through the first 21 days of

treatment (Cycle 1) unless they are considered by the investigator to be clearly unrelated to therapy:

1. Any Grade 5 AE.
2. Any Grade 4 hematologic AE will be considered DLTs except for:
    - Grade 4 lymphopenia that has no clinical sequela, or recovers to Grade ≤2 within 14 days.
    - Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) lasting <48 hours that is not associated with fever (defined as a single temperature >38.3°C or sustained temperature of 38°C for more than 1 hour) or other clinically significant symptoms.
    - Grade 4 hematologic AEs that last <7 days.
3. Platelet count $<10.0 \times 10^9$/L, at any time.
4. Febrile neutropenia: Grade ≥3 neutropenia (ANC $<1.0 \times 10^9$/L) with fever and/or infection.
5. Grade 3 thrombocytopenia lasting longer than 14 days or accompanied by Grade 2 bleeding or requiring transfusion.
6. Any Grade 3 immune-related adverse events such as pericarditis, pneumonitis, cardiotoxicity, hepatitis or neurotoxicity.
7. Grade ≥3 nonhematologic toxicity with the following exceptions:
    - Grade 3 fatigue lasting less than 7 days.
    - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs within 7 days.
    - Grade 3 endocrine disorder that is managed with or without therapy and the patient is asymptomatic.
    - Grade 3 inflammatory reaction attributed to a local antitumor response (tumor flare).
    - Grade 3 IRR that resolves within 6 hours with appropriate clinical management.
    - Grade 3 CRS that resolves to Grade ≤1 in less than 7 days.
    - Asymptomatic nonhematological laboratory changes that are otherwise asymptomatic and that can be controlled to Grade ≤1 or baseline in 7 days with appropriate treatment or with dose interruption and does not result in a delay of >7 days of planned treatment. In this setting, a course of action will be determined jointly by the investigator and the sponsor clinician.
    - Grade 3 elevation in ALT, AST, or alkaline phosphatase that resolves to Grade ≤2 with supportive care within 7 days and is not associated with other clinically significant consequences.

- Isolated Grade 3 electrolyte abnormalities that resolve to Grade ≤2 with supportive care within 7 days and are not associated with other clinically significant consequences.
- Grade ≥3 diarrhea that can be controlled to Grade ≤1 or baseline in 7 days with optimal supportive therapy.
- Grade ≥3 nausea and/or emesis that can be controlled to Grade ≤1 or baseline in 7 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 lasting ≤7 days after treatment that includes topical steroid treatment, oral administration of antihistamines, and pulse oral steroids (if necessary).

8. Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug and dose-limiting.
9. Delay in the initiation of Cycle 2 by more than 14 days due to a lack of adequate recovery of treatment-related hematological or nonhematological toxicities.
10. Missed at least 1 planned dose of TAK-981 or planned dose of pembrolizumab in Cycle 1 due to treatment-related AEs.

8.3 Definition of DLT-Evaluable Patients in Phase 1b

Patients enrolled in Phase 1b are considered evaluable for assessment of a DLT if either of the following criteria is met during the DLT assessment period of 21 days following the first dose of treatment (Cycle1):

- The patient experienced a DLT at any time after receiving the first dose of TAK-981 during the DLT assessment period (Cycle 1).

or

- The patient received all planned TAK-981 doses and 1 administration of pembrolizumab in Cycle 1.

For the Phase 1b part of the study, patients who withdraw before completing the 21-day DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT and will be replaced.

8.4 Phase 1b Dose Escalation Rules

In the Phase 1b portion of the study, only the dosing of TAK-981 will be escalated. Pembrolizumab will be administered at a fixed dose of 200 mg for each scheduled infusion.

The starting dose level of TAK-981 in combination with pembrolizumab will be 40 mg which is 1 dose level below the monotherapy dose that has cleared the DLT period in the ongoing FIH single-agent study (Study TAK-981-1002). The following dose levels of TAK-981 will be potentially considered: 25, 40, 60, 90, 120, and 160 mg. TAK-981 cannot be escalated above the

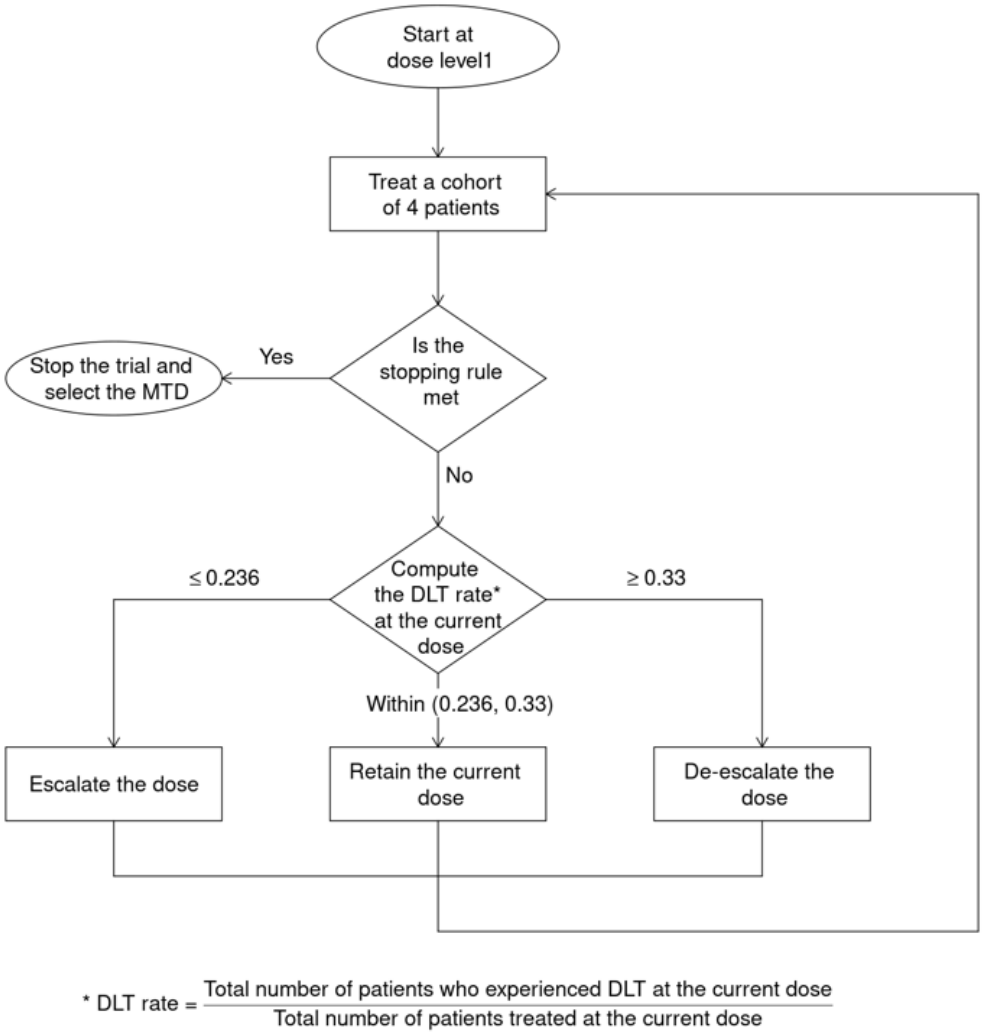
MTD defined in the FIH study or to a maximum dose level of 160 mg, which-ever is lower. Evaluation of lower or intermediate dose levels are permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of toxicity, exposure, or pharmacodynamics of TAK-981.

Dose escalation will follow a BOIN design (Yuan et al. 2016). Approximately 4 patients will be enrolled in the first cohort. The decision to escalate or de-escalate the dose of TAK-981 will be based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the BOIN model. The target DLT rate for this study is 0.3. The dose escalation and de-escalation rules for TAK-981 are as follows.

1. If the observed DLT rate at the current dose level is ≤0.236, escalate.
2. If the observed DLT rate at the current dose level is ≥0.33, de-escalate.
3. Otherwise, stay at the same dose level.

The schema of the dose escalation is presented in Figure 8.a.

Figure 8.a Phase 1b Dose Escalation Schema



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

It is estimated that up to approximately 32 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981. For each cohort of patients enrolled at a given dose level, the observed DLT rate will be calculated for that dose level. If the observed DLT rate at the current dose is ≤0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥0.33, the next cohort of patients will be treated at the next lower dose level. The boundary guiding the number of patients treated at the current dose is displayed in Appendix H in which the operating characteristics of the BOIN design based on 1000 simulations of each scenario are presented.

Alternative dosing schedules for TAK-981 (eg, Day 1, or Days 1, 8, and 15 in 21-day cycles) may be explored in agreement between the investigators and sponsor. TAK-981 escalation for different TAK-981 schedules will be evaluated separately.

Dose escalation and cohort expansion decisions will be determined by the SMC. The SMC will review the Cycle 1 safety of all treated patients and will take into consideration the pattern of irAEs beyond the DLT window across all patients enrolled and make decisions regarding dose escalation. In addition, the available PK and pharmacodynamic information will also be evaluated to support the dose escalation.

8.5 Dose Management and Modification Guidelines

8.5.1 Intrapatient Dose Escalation

Patients in the Phase 1b part of the study with Grade ≤2 toxicity during the previous treatment cycle at the initially assigned dose may have their doses of TAK-981 increased in subsequent cycles of treatment only if all patients in the next dose level cohort have completed assessment for Cycle 1 and a decision has been made that this dose level does not exceed the MTD after agreement between the investigator and the sponsor. The maximal intrapatient dose escalation level will be 1 dose level. Patients in Phase 2 will not have their dose escalated.

8.5.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

A treatment cycle in this study is 21 days. For a new cycle of TAK-981 in combination with pembrolizumab treatment to begin, the patient must meet the following criteria:

- ANC $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 75.0 \times 10^9$/L.

Before starting a new treatment cycle for TAK-981 in combination with pembrolizumab, drug-related AEs or laboratory abnormalities must have returned to Grade ≤1 or baseline or become clinically insignificant as determined by the investigator (unless otherwise specified). If the patient fails to meet the above-cited criterion for retreatment, initiation of the next cycle of treatment of TAK-981 in combination with pembrolizumab should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle be delayed for more than 28 days from the last TAK-981 administration because of incomplete recovery from treatment-related toxicity, the patient must discontinue treatment with TAK-981 unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor.

In case of permanent discontinuation of TAK-981 due to a treatment-related AE as defined in Sections 8.5.3.1 and 8.5.4.1, patients can continue treatment with pembrolizumab alone if the criteria for reinitiating treatment defined in Section 8.5.3.2 are met.

8.5.3 Criteria for Dose Interruption or Dose Reduction

All toxicities that occur during the study will be actively managed following standard of care and/or institutional guidelines unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-981, pembrolizumab, or the combination, may continue study treatment with the same dose, may have the treatment held, or may be permanently discontinued from the study. Patients who have study drugs held because of treatment-related or possibly related AEs should resume study drug treatment according to the dose modification guidelines below. If the dose of 1 study drug is delayed or modified because of toxicity attributed to its use, the dose of the other study drug may be administered as scheduled. If the causality of toxicity is attributed to both study drugs by the investigator, both study drugs should be modified following the dose modification guidelines shown in Table 8.a, Table 8.b, and Table 8.c.

For additional information, refer to the TAK-981 IB and the pembrolizumab Summary of Product Characteristics (SmPC) (Keytruda (pembrolizumab) Injection for Intravenous Use 2023).

8.5.3.1 TAK-981 Dose Modification Guidelines

Dosing of TAK-981 should be interrupted during a treatment cycle or reduced according to the dose modification recommendations listed in Table 8.a for nonhematologic toxicity and Table 8.b for hematologic toxicities. When the dose of TAK-981 is withheld based on the listed criteria, clinical and laboratory reevaluation should be repeated weekly or more frequently, depending on the nature of the toxicity observed until the toxicity resolves to the grade specified in Table 8.a and Table 8.b. If indicated, the TAK-981 dose should be reduced by at least 1 dose level.

If TAK-981 alone or in combination with pembrolizumab cannot be administered within a cycle in a 48-hour window because of an AE, the dose will be missed, and the patient will be scheduled for the next administration per SOE.

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, or there were other circumstances contributing to the AE that are unlikely to recur, the dose may be re-escalated to the original dose level. If more than 2 dose-level reductions of TAK-981 are needed to manage TAK-981-related AEs, treatment with TAK-981 should be discontinued.

Table 8.a General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Treat according to local practice. 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 DL.
Grade 3 and Grade 4 non-life-threatening AEs	Hold TAK-981 until resolution to Grade ≤1 or baseline level, and then resume treatment at the next lower DL, except for the following instances that do not require dose reduction: • Grade ≥3 nausea, vomiting, and/or diarrhea resolved to Grade ≤1 or baseline within 72 hours with optimal antiemetics and/or antidiarrheal following local practice. • Transient Grade 3 fatigue (lasting <72 hours) and asymptomatic Grade ≤4 laboratory abnormalities that the investigator considers not clinically significant following agreement between sponsor and investigators. Note: Permanently discontinue treatment if Grade ≥3 QTcF prolongation, or Grade ≥3 pneumonitis.
Grade 4 life-threatening AEs	Permanently withdraw the patient from treatment with TAK-981.
AEs of all grades	If treatment has been held for >21 consecutive days without resolution of the toxicity (to baseline level or Grade ≤1 or if considered a sequela), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment should be resumed at a reduced DL after resolution of AEs to Grade ≤1 or baseline.

AE: adverse event; DL: dose level.

Table 8.b TAK-981 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN-1.5 × 10^9 cells/L)	Continue TAK-981 at the same DL.
Grade 2 (ANC 1.0- <1.5 × 10^9 cells/L)	Continue TAK-981 at the same DL.
Grade 3 (ANC 0.5- <1 × 10^9 cells/L) without fever	Withhold dose until resolved to Grade ≤2 or baseline, then: • If resolved in ≤7 days, resume treatment at the same DL. • If resolved in >7 days, resume treatment at the next lower DL (ie, reduce by 1 DL).
Grade 4 (ANC <0.5 × 10^9 cells/L) without fever	Withhold dose until resolved to Grade ≤2 or baseline, then resume treatment at the lower DL (ie, reduce by 1 DL).
Febrile neutropenia (ANC <1.0 × 10^9 cells/L, with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than 1 hour)	Withhold dose until fever/infection have recovered and ANC Grade ≤2 or baseline, then resume treatment at the lower DL (ie, reduce by 1 DL).
Thrombocytopenia (PLT)	
Grade 1 (PLT <LLN-75.0 10^9 cells/L)	Continue TAK-981 at the same DL.
Grade 2 (PLT <75.0 - 50.0 × 10^9 cells/L)	Continue TAK-981 at the same DL.
Grade 3 (PLT <50.0 - 25.0 × 10^9 cells/L) without bleeding	Withhold dose until resolved to Grade ≤1 or baseline, then: • If resolved in ≤7 days, resume treatment at the same DL. • If resolved in >7 days, resume treatment at the lower DL (ie, reduce by 1 DL).
Grade 4 (PLT <25.0 × 10^9 cells/L) without bleeding	Withhold dose until resolved to Grade ≤1 or baseline, then resume treatment at the lower DL (ie, reduce by 1 DL).
Platelets <10.0 × 10^9 cells/L, thrombocytopenia Grade ≥3 associated clinically significant bleeding	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor, then resume treatment at the lower DL (ie, reduce by 1 DL).

ANC: absolute neutrophil count; DL: dose level; LLN: lower limit of normal; PLT: platelet.

Table 8.c TAK-981 Dose Modification Guidelines for CRS

ASTCT Grade	TAK-981 Dose Modification
Grade 1: Fever [a] (≥38°C)	Continue TAK-981 at the same dose.
Grade 2: Fever [a] (≥38°C) with hypotension not requiring vasopressors; and/or [b] hypoxia requiring low-flow [c] nasal cannula	Withhold dose until resolved to Grade ≤1, then: • If resolved in ≤14 days, maintain DL. • If resolved in >14 days or repeat event, reduce by 1 DL. • If >2 consecutive doses of TAK-981 are skipped due to CRS, permanently discontinue treatment with TAK-981.
Grade 3: Fever [a] (≥38°C) with hypotension requiring a vasopressor with or without vasopressin; and/or [b] hypoxia requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask	Withhold dose until resolved to Grade ≤1, then: • If resolved in ≤14 days, reduce by 1 DL and if toxicity does not recur, consider re-escalating to original DL. • If resolved in >14 days or repeat event, reduce by 1 DL. • If >2 consecutive doses of TAK-981 are skipped due to CRS, permanently discontinue treatment with TAK-981.
Grade 4: Fever [a] (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin); and/or [b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Permanently discontinue TAK-981.

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; DL: dose level.

ASTCT consensus grade adapted from Lee et. Al. 2019 (Lee et al. 2019); CRS management recommendations are adapted from Neelapu et al, 2018 (Neelapu et al. 2018) and should be implemented at the investigator's discretion.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

8.5.3.2 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 (Keytruda (pembrolizumab) Injection for Intravenous Use 2023) other than irAEs may continue TAK-981 treatment.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade ≤1 and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after the AE severity has been reduced 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.
3. 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.

Table 8.d Pembrolizumab Dose Modification Guidelines for irAEs

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	Immune-Related AE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Patients with Grade ≥2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST/ALT elevation or increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently) until liver enzyme value returned to baseline or is permanently stable.
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

Table 8.d Pembrolizumab Dose Modification Guidelines for irAEs

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	Immune-Related AE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Type 1 diabetes mellitus or hyperglycemia	Newly onset Type 1 diabetes mellitus or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for patients with Type 1 diabetes mellitus. Administer antihyperglycemic in patients with hyperglycemia.	Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2 Grade 3 or 4	Withhold Withhold or permanently discontinue [a]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2 Grade 3 or 4	Continue Withhold or permanently discontinue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 2 to 4	Continue	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of thyroid function
Nephritis and renal dysfunction	Grade 2 or 3 Grade 4	Withhold Permanently discontinue	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes in renal function
Myocarditis	Grade 1 Grade 2, 3 or 4	Withhold Permanently discontinue	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes

Table 8.d Pembrolizumab Dose Modification Guidelines for irAEs

Immune-Related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	Immune-Related AE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold [b]	As clinically indicated.	Monitor changes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre syndrome, 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; DRESS: drug rash with eosinophilia and systemic symptoms; GI: gastrointestinal; irAE: immune-related adverse event; IV: intravenous; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; ULN: upper limit normal.

For patients with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy or when metabolic control has been achieved (in case of Type 1 diabetes).

[a] Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.

[b] Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

8.5.4 Criteria for Discontinuation of Treatment With Study Drugs

Patients should discontinue treatment with either TAK-981 or pembrolizumab or both, if they meet the criteria listed below. Patients who discontinue pembrolizumab may continue TAK-981 treatment as a single agent if TAK-981 discontinuation criteria are not met; patients who discontinue TAK-981 may continue pembrolizumab as a single agent if pembrolizumab discontinuation criteria are not met. In the event of discontinuation of study therapy (TAK-981 and pembrolizumab), patients will undergo the EOT visit.

8.5.4.1 TAK-981

Treatment with TAK-981 must be discontinued for any of the following reasons:

- Occurrence of a DLT in dose escalation during the first cycle (exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit/risk assessment).
- Occurrence of drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.5.
- If subsequent cycle is delayed by >21 days for treatment-related AEs despite supportive treatment per standard clinical practice. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit/risk assessment.)
- If more than 2 dose-level reductions of TAK-981 are required for a patient. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit/risk assessment.)
- Occurrence of AEs resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the patient (if applicable).

8.5.4.2 Pembrolizumab

Pembrolizumab will be discontinued if any of the criteria described in dose modification Table 8.d or the 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 times the ULN or total bilirubin greater than 3 times the ULN.
  - For patients with liver metastasis 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.
- 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 adverse reaction that recurs.

8.5.4.3 COVID-19 Infection

If a patient is diagnosed with COVID-19 infection while on study, study treatment must be withheld until resolution of the infection. A patient may restart study treatment if the following criteria are met; otherwise the patient must discontinue treatment:

- The infection must have resolved without ongoing clinical sequalae.
- There should be 2 sequential negative SARS CoV-2 tests 12 hours apart. If necessary, discuss a path forward with sponsor considering PCR tests may continue to be positive for prolonged period of time (Qu et al. 2020) (Plebani 2021) (cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html, Center for Disease Control. Ending Isolation and Precautions for People with COVID-19: Interim Guidance. Jan 14, 2022. Access 22 April 2022).
- The patient must be asymptomatic, and the investigator must believe, with agreement of the sponsor, that the patient would benefit from resuming study treatment.

8.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Prophylactic use of myeloid growth factors (eg, G-CSF) is not allowed in Cycle 1 during dose escalation. Patients who experience severe (ie, Grade 4) neutropenia or febrile neutropenia can be managed with growth factor support, if needed, in accordance with American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. GCSF should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation.
- Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin, but initiation of new erythropoietin therapy is not allowed during the first cycle.

- Any investigational agent other than TAK-981 or pembrolizumab.
- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, or radiation therapy except for palliative radiation therapy and once progressive disease [PD] is ruled out) or standard or investigational agents other than pembrolizumab for treatment of cancer.
- Concomitant corticosteroid administration of >10 mg of prednisone or equivalent unless given as treatment or prophylaxis for IRRs or de novo irAEs, as premedication for administration of certain blood products (80 mg methylprednisolone is accepted) or short courses (<96 hours) for exacerbations of respiratory tract disorders or for acute control of emerging tumor pain.
- Strong and moderate CYP3A4/5 inhibitors and inducers (Appendix E). During the study, should patients require the use of medications that are known to be strong and moderate inhibitors/inducers of CYP3A4/5, they should temporarily discontinue the use of TAK-981. These patients can resume treatment with TAK-981 approximately 1 week after discontinuing the use of these strong and moderate inhibitors CYP3A4/5, and approximately 2 weeks after discontinuing the use of strong and moderate inducers of CYP3A4/5.
- Strong inhibitors of Pgp (Appendix F).
- Because the safety of immunization with live viral vaccines following TAK-981 therapy has not been studied, vaccination with live virus vaccines is not recommended while the patient is being treated on study.
- For patients enrolled in Phase 1, vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs.

8.7 Permitted Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient from their informed consent through the 30 (+10) days follow-up visit after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) will be recorded in the designated electronic case report form (eCRF). Patients must be instructed not to take any medications, including over the counter medications and herbal supplements, without first consulting with the investigator.

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

- Myeloid growth factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor) and/or erythropoietin support, as clinically indicated.
- Topical, intranasal, or inhaled steroids (eg, for the treatment of asthma).
- Patients should be transfused with RBCs and platelets as clinically indicated.

- Concomitant treatment with bisphosphonates will be allowed for patients with evidence of lytic destruction of bone or with osteopenia, according to the ASCO Clinical Practice guidelines or institutional practice in accordance with the product label, unless specifically contraindicated.
- Local radiation of isolated lesions for palliative intent (for example, pain control) is acceptable provided that the requirement for radiation does not represent a progression of the disease and that the radiated lesion is not a target lesion.
- Narrow therapeutic range Pgp substrates such as digoxin or dabigatran may be used with caution, and patients requiring use of these drugs will be closely monitored.
- COVID-19 vaccination is generally allowed for patients enrolled in the study with the exception of live attenuated vaccines which must be completed at least 4 weeks prior to treatment initiation. COVID-19 vaccination should follow local guidances and regulations. Ideally, patients will have completed vaccination prior to treatment initiation. For patients enrolled in Phase 1, vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs. Vaccination should be avoided within ±3 days of TAK-981 administration and should be administered after the last dose of TAK-981 of a given cycle; study treatment may be delayed for up to 7 days to accommodate a vaccine dose administration after discussion with the Sponsor. Vaccination should be captured as a concomitant medication.

Additional concomitant medications and procedures are permitted during the study to prevent and actively manage AEs related or not related to the study drug(s) unless prohibited as specified in this protocol. Supportive measures consistent with optimal patient care may be given throughout the study.

8.8 Precautions and Restrictions

It is not known what effects TAK-981 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (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.)

Before starting treatment, male patients should be advised to seek counseling on sperm storage, and female patients should be advised to seek counseling on egg storage.

8.9 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, granulocyte colony stimulating factor, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology/ASCO guidelines or local institutional practice. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.5.

The sections below provide guidance for the management of some expected AEs based on observations in nonclinical toxicology or other AEs that have not been substantiated in these experiments but that could be expected because of the mechanism of action of TAK-981, and warnings and precautions in the pembrolizumab SmPC. This guidance is not expected to replace investigator judgment in the management of AEs.

8.9.1 Nausea or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a short course of corticosteroid given in standard doses and according to standard schedules. If these are inadequate, an NK-1 antagonist may be added.

8.9.2 Diarrhea

This study will not initially employ prophylactic antidiarrheals. Patients in this study must be monitored for immune-mediated colitis and treated per local guidance.

8.9.3 Anemia, Thrombocytopenia, or Neutropenia

Please refer to Table 8.b for dose delay and reduction recommendations for hematologic toxicities. TAK-981 should be withheld if a significant treatment-emergent cytopenia or bleeding is suspected to be related to, or could be worsened by, study treatment. Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBCs or platelet) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/thrombocytopenia at the discretion of the investigator per standard clinical practice. Use of myeloid growth factor (eg, granulocyte colony stimulating factor) support to treat Grade ≥3 neutropenia and/or febrile neutropenia is recommended per regional guidelines or local institutional practice; prophylaxis is permitted per regional guidelines or local institutional practice.

8.9.4 Infusion Site Care

Skin lesions, which may include inflammation or necrosis, represent a potential risk of TAK-981 and were observed at the injection site in rats. Local institutional guidelines must be applied to stress proper administration and prevention of accidental extravasation of TAK-981. Usage of an IV port is highly recommended. The IV line should be flushed at the end of the infusion according to local procedures. Monitoring at the beginning of and during infusion must be ensured. If extravasation occurs, the infusion must be discontinued immediately and institutional guidelines applied. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. Patients should be instructed to report any discomfort, pain, or swelling at the infusion site.

8.9.5 Lymphopenia and Opportunistic Infection Prophylaxis

Because lymphopenia is an expected TAK-981-related AE, patients may be at an increased risk of opportunistic pathogens. Follow-up with standard hemograms and serial immunophenotyping will help to make clinical decisions about the risk of immunosuppression.

Prophylaxis for PJP should be initiated if the following is present:

- Absolute CD4+ T-cell count of <200/mm^3.
- Percent CD4+ T-cells <20%.
- Prior episode of PJP in medical history.

For older patients or patients who, in the investigator's opinion, are more susceptible to opportunistic infection at baseline, PJP prophylaxis should be considered at the start of study treatment. When steroids or any immunomodulatory agents need to be used to manage AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is co-administered. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated; however, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

In the event of long-lasting lymphopenia, pneumocystis, or herpes zoster infection, prophylaxis can be started at the investigator's discretion.

8.9.6 IRRs

Although TAK-981 is not a biologic drug, its immune-activating properties may also produce AEs in the category of IRRs. If such reactions were to occur, they might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. Treatment and monitoring of patients presenting with IRRs to TAK-981 or pembrolizumab until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. If an IRR develops during the TAK-981 or pembrolizumab infusion, the patient should be closely monitored until recovery of symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and communicated as an SAE if criteria are met. Concomitant medications administered for infusion reaction treatment should be collected in the eCRF. If a patient presents signs and symptoms compatible with infusion reaction on days on which just TAK-981 is given, and at investigator discretion, premedication can be instituted for the remaining TAK-981 doses.

8.9.7 CRS

CRS is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. CRS should be diagnosed and managed following institutional guidelines and graded following ASTCT Consensus Grading for CRS (Lee et al. 2019). Investigators should try to differentiate CRS from other IRRs. Recommendations for management of CRS are shown in Table 8.e and can be implemented at the investigator's discretion. Table 8.c also provides indications for dose modifications after a CRS event.

Table 8.e CRS Management Recommendations

ASTCT Consensus Grade	CRS Management Recommendations
Grade 1: Fever [a] (≥38°C)	Monitor fluid status. Supportive care: antipyretics, analgesics.
Grade 2: Fever [a] (≥38°C) with hypotension not requiring vasopressors; and/or [b] hypoxia requiring low-flow [c] nasal cannula	As per Grade 1 and: • Closely monitor all organ functions, including cardiac function. • IV fluid bolus. • Supportive care.
Grade 3: Fever [a] (≥38°C) with hypotension requiring a vasopressor with or without vasopressin; and/or [b] hypoxia requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask	As Grade 2 and: • Closely monitor all organ functions, including cardiac function. • Tocilizumab (8 mg/kg IV; maximum dose 800 mg) can be repeated after 6 hours. • If refractory to tocilizumab, dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg every 6 hours or equivalent methylprednisolone. • Vasopressors as needed. • Supplemental oxygen as needed for hypoxia (including high-flow O_2 and CPAP). • Transfer to ICU.
Grade 4: Fever [a] (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin); and/or [b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	As per Grade 3 and: • Substitute dexamethasone with methylprednisolone 1 g IV per day. • Mechanical ventilation.

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; ICU: intensive care unit; IV: intravenous; O_2: supplemental oxygen.

ASTCT consensus grade adapted from Lee et al, 2019 (Lee et al. 2019); CRS management recommendations are adapted from Neelapu et al, 2018 (Neelapu et al. 2018) and should be implemented at the investigator's discretion.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

8.9.8 Management of Immune-Mediated AEs

Pembrolizumab and TAK-981 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 dose escalation and expansion cohorts in the combination arm. Patients with AEs that are suspected to be related to pembrolizumab or TAK-981 should be evaluated by appropriate methodology, including physical examinations, laboratory tests, and imaging. These irAEs will be treated based on SOC, local institutional guidance, the WARNINGS AND PRECAUTIONS section of the package insert, and the proper use guidance of pembrolizumab and TAK-981 dose modifications.

8.10 Blinding and Unblinding

This is an open-label study.

8.11 Description of Investigational Agents

TAK-981

TAK-981 drug product has been developed as an injection, for IV use (solution for infusion). CCI [redacted] It is packaged in a glass vial containing 10 mL of TAK-981 sterile solution, with 0.5 mL excess volume.

For specific information about the storage and handling of TAK-981 drug product, refer to the study or pharmacy manual associated with a given study protocol or the Instructions for Use contained in the shipping package.

Full details are available in the IB.

Pembrolizumab

Pembrolizumab solution for injection 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.

8.12 Preparation, Reconstitution, and Dispensation

TAK-981

The reconstituted product will be administered by IV infusion over 1 hour (±10 minutes). After the end of the infusion the IV line should be flushed accordingly to local standards. Detailed reconstitution and dosage preparation instructions are provided in the directions for use located in the pharmacy manual.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

TAK-981 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-981.

Reconstituted study products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Pembrolizumab

Please refer to the pharmacy manual and/or the most recent SmPC for preparation, reconstitution, and administration instructions.

A commercially available IV formulation of pembrolizumab background therapy will be used. The sponsor will provide commercial supplies of pembrolizumab for IV administration, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Patients enrolled in countries where pembrolizumab is designated as non-investigational product, should obtain commercially available product through the local hospital pharmacy or licensed distributor. Patients enrolled in countries where pembrolizumab is designated as investigational product, will have pembrolizumab supplied and packaged by the sponsor.

8.13 Packaging and Labeling

All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.14 Storage, Handling, and Accountability

TAK-981

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained for all used and unused study drug vials. A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients, will be provided and kept at the study site. Disposal instructions are provided in the pharmacy manual.

The required storage condition for TAK-981 study drug is -20°C ± 5°C. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-981 received and that any discrepancies are reported and resolved before use of TAK-981.

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.

8.15 Other Protocol-Specified Materials

Information on supplies required by the site for drug administration is provided in the pharmacy manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the study manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (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, and other vendors such as the interactive response technology provider, may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

For 24-hour contact information, please refer to the study manual or equivalent.

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 institutional review board (IRB). Prisoners (or other populations that might be subject to coercion or exploitation) will not be enrolled into this study.

9.3 Treatment Group Assignments

This is not a randomized study. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study. Details can be found in the cohort management plan.

9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, EOT visit, two follow-up visits at 30 and 90 days (+10 days) after the last dose, PFS follow-up visits for patients who discontinued for reasons other than PD, and follow-up for OS for patients in Phase 2, for a maximum of 12 months for each patient after their last dose of study drug to monitor disease and survival status. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of the study drug. Procedures conducted during the screening period that are performed within 3 days of C1D1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified.

Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. The timing of PK and pharmacodynamic assessments is specified in the SOE

(Appendix A). Laboratory assessments and procedures may occur up to 3 days before the scheduled day. For image tests (CT scan, positron emission tomography [PET] with ^{18}fluorodeoxyglucose [FDG-PET], MUGA, ECG), a ±7-day window is allowed.

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 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.

9.4.2 Patient Demographics

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

9.4.3 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. In addition, concomitant medications will be recorded as specified in Section 9.4.8.

Available tumor pathology/cytogenetic/mutational information, such as driver mutations/alterations (eg, *EGFR, ALK, ROS1, RET, MET, ATM, BRCA1/2, NTRK, KRAS, BRAF*), HPV status, and tumor mutational burden, and PD-L1 results among others, should be reported for all patients in the eCRF.

PD-L1 tumor status is required from all patients in Phase 2. If the patient requires immediate treatment and PD-L1 testing result is not available before the start of treatment, medical monitor or designee approval for initiation of protocol treatment is required; in this case, submission of an appropriate sample (either archival tissue or pretreatment biopsy) for local testing is required.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A). Any clinically relevant findings are to be documented.

9.4.5 Patient Height and Weight

Height and body weight will be measured at the times specified in the SOE.

9.4.6 Vital Signs

Vital signs (blood pressure, heart rate, and temperature) will be monitored as specified in the SOE (Appendix A).

9.4.7 Pregnancy Test

A serum or urine pregnancy test will be obtained for women of childbearing potential at screening, Day 1 of each cycle, and at the EOT. The screening result must be available and negative before enrollment and dosing. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

9.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent through the follow-up visit 30 days (+10 days) after the last dose of study drug in case of treatment discontinuation, or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.6 for a list of medications and therapies that are prohibited during the study.

9.4.9 AEs

Monitoring of AEs, serious and nonserious, will be conducted from the time of informed consent throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.10 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug.

Procedures for completing enrollment information are described in the study manual.

9.4.11 Cardiac Monitoring

A single 12-lead standard safety ECG will be performed to assess eligibility as specified in the SOE (Appendix A). ECG assessments are to be performed with the patient rested for at least 5 minutes before collection. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

The assessment of LVEF measured by echocardiography or MUGA will be performed as indicated in SOE. From Cycle 3 onwards, a ±7-day window is allowed for this test. When the timing of ECG or vital sign measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first followed by blood sampling.

9.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Additional handling and shipment of clinical laboratory samples will be outlined in the study manual.

9.4.12.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the chemistry and hematology parameters shown in Table 9.a, urine samples for analysis of the parameters shown in Table 9.b, and tumor prognostic markers

shown in Table 9.c will be obtained as specified in the SOE (Appendix A). They will be performed locally only.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	Activated partial thromboplastin time (aPTT)
Hemoglobin	Alkaline phosphatase	Prothrombin time (PT)
Leukocytes with differential ANC	Alanine aminotransferase	Fibrinogen
CD4/CD8 count and ratio	Aspartate aminotransferase	
Platelets (count)	Bilirubin (total)	
	(Blood) Urea nitrogen (BUN)	
	Calcium	
	Bicarbonate ($HCO3^-$) or Carbon dioxide (CO_2)	
	Creatinine	
	(Standard) C Reactive protein	
	Chloride	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Protein (total)	
	Urate	

ANC: absolute neutrophil count.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	Urine pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Urobilinogen
Nitrite	
Occult blood	

Table 9.c Tumor Prognostic Markers

Colon Cancer	Cervical Cancer
Carcinoembryonic antigen (CEA)	Cancer antigen 15-3 (CA 15-3)
Cancer antigen 19-9 (CA 19-9)	Cancer antigen 125 (CA 125)

Blood sample collection for tumor markers during Phase 2 only.

Hematology, chemistry, coagulation testing, and urinalysis samples may be taken up to 3 days before the visit (unless otherwise specified) and may be conducted 24 hours before the visit. All results must be evaluated before dosing. Microscopic analysis of urine sediment should be performed if significant abnormalities are detected in proteins, leukocytes, or blood.

Serum creatinine clearance is to be estimated by the Cockcroft-Gault formula (Cockcroft and Gault 1976) as follows:

$$\text{Estimated creatinine clearance} = [(140 - \text{Age}) * \text{Mass(kg)}\ ] / [72 * \text{serum creatinine(mg/dL)}]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.12.2 Immunosafety Markers

Blood samples for the analysis of autoimmune endocrinopathies as shown in Table 9.d will be obtained as specified in the SOE (Appendix A). They will be performed locally only. Results may be evaluated after dosing.

Table 9.d Immunosafety Determinations in Serum

Serum Chemistry	
Thyrotropin (TSH)	Free thyroxine (FT4)
	Adrenocorticotropic hormone (ACTH)

9.4.13 Disease Assessment

Patients will undergo CT and/or magnetic resonance imaging (MRI) scans, and/or FDG-PET imaging to assess disease response and progression, using RECIST, Version 1.1 (Eisenhauer et al. 2009). For this study CT and/or MRI scans should be acquired with at least IV contrast. CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. 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 non-contrast CT of the chest, in addition to contrast-enhanced abdomen, and pelvis MRI images should be acquired, if possible. Anatomical measurements (individually and summed across target lesions) will be collected at baseline and each subsequent evaluation. In addition, non-measurable disease and new lesions will be documented and their status evaluated.

Bone and PET scans should be collected as clinically indicated. Objective assessments of the disease burden: target, non-target, and potential new lesions, will be performed at each time point (a ±7-day window is allowed for image tests) as described in the SOE (Appendix A). For Phase 2, radiographic images will be collected centrally. Test results and physician findings will be filed in patient source documents. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction. Objective response data collected for the clinical study report will be based on investigator assessment.

Imaging tests performed before the screening consent date may be used as screening tests if C1D1 is planned within the 28 days after the date of the test.

9.4.13.1 Modified RECIST, Version 1.1 for Immune-Based Therapeutics (iRECIST) and Treatment Beyond Progression:

For patients who have initial radiological evidence of PD by RECIST, Version 1.1 as determined by the site, the investigator may elect to continue a patient on study treatment until repeat imaging is obtained (iRECIST-based management) (Seymour et al. 2017). This clinical judgment decision by the investigator should only be made if the patient is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such patients may continue to receive study treatment and an imaging-based tumor assessment should be repeated ≥ 4 weeks later in order to reassess PD per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (eg, central nervous system metastasis with potential for cord compression).

Note: Patients exhibiting toxicity from study treatment as outlined in Section 8.5.4 may NOT continue to receive trial therapy.

In determining whether or not the tumor burden has increased or decreased per iRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

iRECIST defines unconfirmed progressive disease (iUPD) on the basis of RECIST, Version 1.1 principle; however, iUPD requires confirmation obtained by repeat imaging at least 4 weeks, but no longer than 8 weeks after.

9.4.13.1.1 Confirming Progression

Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

A. Immune-confirmed progressive disease (iCPD) is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST, Version 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions.
- Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
- Continued unequivocal progression in non-target disease with an increase in tumor burden.
- Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

OR

B. RECIST, Version 1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or immune stable disease (iSD), immune partial response (iPR) or immune complete response (iCR) if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD (Seymour et al. 2017).

9.4.13.1.2 New Lesions

New lesions should be assessed and measured as they appear using RECIST, Version 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as new lesions-target (NLT) and new lesion-non-target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the eCRF.

PD is confirmed in the new lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with

either an increase of at least 5 mm in the absolute value of the sum of NLT, an increase (but not necessarily unequivocal increase) in the size of NLNT lesions or the appearance of additional new lesions.

9.4.14 Biomarker, Pharmacodynamic, and PK Samples

9.4.14.1 Primary Specimen Collection

The primary specimens to be collected are shown in Table 9.e. Collection of samples for exploratory endpoints are dependent upon local guidelines and regulations (including feasibility of sample export), as well as IRB/independent ethics committee (IEC) approval.

Table 9.e Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
Archival (banked) tumor tissue sample	FFPE block FFPE slides	DNA RNA		Biomarker measurements	Required if ≤12 months
Fresh tumor tissue biopsy sample at Screening	Fresh tumor tissue	FFPE block/slides	DNA RNA	Biomarker measurements	Mandatory.
Paired fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block/slides	DNA RNA	Biomarker measurements	Optional.
Plasma sample for chemokines	Plasma			Biomarker measurements	Mandatory
Blood cells for immunophenotyping	Blood	Cells		Biomarker measurements	Mandatory
PBMCs sample for immunophenotyping [a]	Blood	Cells		Biomarker measurements	Mandatory in Phase 1b
Blood sample for flow cytometry (adduct/conjugate)	Blood	Cells		Biomarker measurements	Mandatory in Phase 1b
Blood sample for RNA	Blood	RNA		Biomarker measurements	Mandatory
Serum sample for circulating biomarkers	Serum			Biomarker measurements	Mandatory in Phase 1b
Blood sample for DNA	Blood	DNA		Biomarker measurements	Mandatory in Phase 1b
Blood sample for cfDNA	Plasma	DNA		Biomarker measurements	Mandatory
Plasma sample for TAK-981 PK	Plasma			PK measurements	Mandatory

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

[a] This term has been updated from "Blood sample for immunophenotyping" to "PBMCs sample for immunophenotyping" for the purpose of standardization; however, the previous term may continue to be utilized by the central laboratory in the labeling of these samples.

9.4.14.2 Tumor Biopsies

For patients in Phase 2, baseline (pretreatment) tumor collection is mandatory. Pretreatment fresh tumor biopsy at screening can be replaced by a recent (≤12 months old) formalin fixed paraffin embedded tumor specimen. For fresh tumor biopsies, the lesion must be accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal, or obtained with endoscopic procedures beyond the stomach or bowel). Either a fresh tumor biopsy or banked tumor taken within 12 months of enrollment is required. This sample will be assessed for other features of the tumor and/or tumor microenvironment including immune cell content and tumor mutations.

The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of study drug. On-treatment tumor biopsy for patients who have provided a fresh tumor tissue sample during screening will be encouraged but optional. The on-treatment biopsy will be obtained after TAK-981 infusion on C2D8 (+7 days). The accessible lesion biopsy (screening and on-treatment) should not have been previously designated as the only target lesion for measurable disease or located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible. On-treatment biopsy collection visit day may be changed if data emerges that would be supportive of such change.

When provided, paired tumor biopsies will be used to determine TAK-981-SUMO adduct formation and SUMO pathway inhibition in the tumor, as well as activation markers and markers of functional modulation of the immune response in the tumor/TME. Induction of an innate and/or adaptive immune response and check point modulation in the tumor and TME will be by measuring levels of PD-1 and PD-L1 expression and activation state of tumor-infiltrating lymphocytes and myeloid cells, including NK cells and macrophages.

Hematology and coagulation tests including platelet counts, international normalized ratio and activated partial thromboplastin time (aPTT) should be performed prior to a biopsy procedure being performed and the risk of bleeding associated with the procedure must be assessed by the investigator.

9.4.14.3 Banked Tumor

Archival (banked) tumor tissue sample block or approximately 10 unstained slides collected within 12 months of study initiation will be collected when available from all enrolled patients to assess baseline features such as gene mutations, gene signatures, gene expression, tumor mutation burden, immune cell content and their spatial relationships, or biomarkers of response or resistance to TAK-981, pembrolizumab or their combination that may emerge from future nonclinical or clinical studies. See the laboratory manual for details.

9.4.14.4 Fresh Paired Tumor Biopsy

Paired screening and on-treatment biopsies are highly encouraged (but optional) for all patients in the study. The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of

study drug. The on-treatment biopsy will be obtained post-TAK-981 infusion on C2D8 (+7 days). The accessible lesion biopsy (screening and on-treatment) should not have been previously designated as the only target lesion for measurable disease or located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible. On-treatment biopsy collection visit day may be changed should data emerge that would be supportive of such change.

9.4.15 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual. Plasma samples for TAK-981 PK will be collected at the time points specified in Appendix A. Blood/plasma samples should be collected from the contralateral arm (not the arm which was used for drug infusion).

The timing but not the total number of plasma samples may be modified during the study based on emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK of TAK-981. A protocol amendment is not necessary for such modifications.

9.4.16 Pharmacodynamic Measurements

The pharmacodynamics specimen collection time points are displayed in the SOE (Appendix A). Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

The following pharmacodynamic measures will be tested:

- TAK-981-SUMO adduct formation and SUMO2/3 inhibition in blood, and paired tumor biopsies (when collected).
- Chemokines and cytokine analysis in plasma, including those in the IFN pathway.
- Immunophenotyping in whole blood, peripheral blood mononuclear cells (PBMCs, when collected), and paired tumor biopsies (when collected).
- Gene expression analysis, including IFN pathway, in whole blood

9.4.17 DNA Measurements

As detailed in the SOE (Appendix A), whole blood will be collected predose on C1D1 as a germline control sample for DNA mutation analysis from banked tumor and/or fresh tumor biopsies. Plasma samples will be collected as per SOE for evaluation of cfDNA to assess tumor mutations over time. In addition, the extracted DNA from such samples may be used in pharmacogenomic evaluation to study the impact of genetic polymorphism in drug metabolizing enzymes and/or transporters that may be implicated in the disposition of TAK-981 or response to anti-PD-1 therapies. The data resulting from such analyses, if performed, may be pooled with similar data from other clinical studies for eventual population PK analysis purposes and as such will be reported separately and not within the clinical study report for this study.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment when they have discontinued treatment with both study drugs, TAK-981 and pembrolizumab.

9.6 Completion of Study (for Individual Patients)

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

- Death.
- PD per iRECIST.
- Start of new systemic treatment.
- Withdrawal by patient.
- Study terminated by the sponsor.
- Lost to follow-up.
- Transfer of patient to a TAK-981 long-term safety study, single-patient investigational new drug application, or similar program.

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

9.7 Discontinuation of Treatment With Study Drugs and Patient Replacement

Patients will be informed that they have the right to discontinue study treatment at any time for any reason, without prejudice to their medical care. It is possible that 1 study drug is permanently discontinued due to treatment-related AEs, while the patient continues to receive the other study drug and remains on treatment. Discontinuation of treatment occurs only when both study drugs are required to be discontinued due to AEs or upon the occurrence of any of the other non-AE criteria.

Treatment with study drug may be discontinued for any of the following reasons:

- Withdrawal by patient.
- Occurrence of a DLT for patients in dose escalation (exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit/risk assessment).
- AE that leads to TAK-981 and pembrolizumab discontinuation.
- Occurrence of drug-related AEs that require discontinuation of study drug(s) per dose modification guidelines in Section 8.5.3.1.
- Treatment interruption of more than 63 days (3 cycles) for study drug-related or possibly related AEs.

- Symptomatic deterioration.
- PD per iRECIST.
- Death.
- Pregnancy.
- Major protocol deviation.
- Initiation of another systemic anticancer treatment.
- Study terminated by sponsor.
- Treatment completion.
- Lost to follow-up.

9.7.1 Treatment Beyond Progression

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach can manifest as a clinical response after an initial apparent increase in tumor burden (ie, pseudoprogression) or even the appearance of new lesions. Standard RECIST, Version 1.1-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents. For this reason, the modified iRECIST criterion of iCPD will be required before treatment discontinuation. Therefore, in the event of PD by RECIST, Version 1.1 that is also considered iUPD, repeat disease imaging will be performed at 4 to 8 weeks, and if the investigator determined that the patient is clinically stable, treatment with study drugs should not be discontinued until iCPD is declared.

Once TAK-981 and pembrolizumab have been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF. After the EOT, each patient will be followed for 30 and 90 days (+10) as outlined in the SOE (Appendix A).

9.7.2 Patient Replacement

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) until PD occurs.

During dose escalation, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

In the case of study termination by the sponsor, eligible patients may have continued access to TAK-981 as described in Section 6.6.5.

9.8 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.

9.9 Posttreatment Follow-up Assessments (Survival)

Patients who complete treatment or stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 ± 1 weeks from last dose of study drug until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, or study termination (Section 9.6), whichever occurs first.

The duration of follow-up for PFS, and OS (Phase 2 only) for a patient will be for up to 12 months.

NOTE: During this period, related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths or SAEs that the investigator considers related to study drug that occur during 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.

All abnormal laboratory values will be reviewed by the investigator but only those abnormal values that lead to discontinuation or delay in treatment, dose modification, therapeutic intervention, or are considered by the investigator to be a clinically significant change from baseline, will be assessed as AEs.

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 27 November 2017 (NCI 2017), except CRS that will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). 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 Event of Special Interests Definition

An adverse event of special interest (AESI) is an AE of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in

order to characterize and understand them. Communication between the sponsor and other parties (eg, regulators) will follow regular reporting timelines (ie, 7 days for fatal or life-threatening SUSARs [suspected unexpected serious adverse reactions] and 15 days for other serious events).

A list of AESIs specific to study drugs are provided in Section 10.2.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient 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 a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) 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. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. 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, then 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.

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 the patient was enrolled in the trial *or* 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 27 November 2017 (NCI 2017), except CRS that will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). 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?

AESI Reporting:

The below list of immune-mediated AEs will be treated as AESIs.

- Pneumonitis.
- Hepatitis.
- Colitis.
- Endocrinopathies.
  - Thyroid disorders.
  - Adrenal insufficiency.
  - Type 1 diabetes mellitus.
  - Hypophysitis.
- Nephritis.
- Dermatologic reactions.

All AESIs regardless of seriousness and causality must be reported by the investigator to the sponsor within 72 hours of becoming aware of the event. This will be done by transmitting an EDC. If the AESI meets any of the seriousness criteria mentioned in Section 10.1.3, the event will be reported to the sponsor within 24 hours of the investigator becoming aware of the event. All non-serious AESIs are captured only in the clinical database.

The investigator must follow institutional guidelines to manage immune-mediated AEs.

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 start of a new systemic treatment, 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 and recorded in the eCRF. 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 due to a patient's stable or chronic condition or intercurrent illness(es).
- AESIs will be reported and monitored from C1D1 through the 90-day visit or until resolved.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. If transmission of a pregnancy report is not feasible, then a facsimile of the completed Takeda paper-based pregnancy form will be sent.

Pregnancies are to be reported through 6 months after the last dose of study drug.

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 email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and 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 email address provided below.

Product	Call Center	Email
TAK-981	Takeda	ctmcomplaint@takeda.com

Product complaints and medication errors 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 and any other applicable SAEs to regulatory authorities, including investigators and IRBs, as applicable, in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 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 study. The investigational site also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Safety Monitoring Committee

During Phase 1b, an SMC composed of the principal investigators, and sponsor clinician will regularly review safety data to ensure patients' safety throughout the study and make decisions on dose escalation as defined in the SMC charter.

11.2 Independent Data Monitoring Committee

During Phase 2, an IDMC will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study. The IDMC will consist of 3 to 5 members not associated with the conduct of the study and/or the sponsor with the exception of the compensation to IDMC members related to their IDMC activities. The IDMC members will be a multidisciplinary group that will include at least 2 oncologists with extensive experience in clinical study conduct and a biostatistician with substantial experience in the IDMC process. The committee will perform data review to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study. IDMC meetings will be held on a periodic basis as defined in the IDMC charter and at the end of each stage of the Phase 2. Ad hoc IDMC meetings may also be held if a significant issue should arise.

11.3 Independent Review Committee

All imaging performed to assess response to treatment will be submitted to a central core imaging repository. An independent review committee (IRC) will be established to independently review efficacy imaging endpoints once any cohort in Phase 2 meets the efficacy threshold in Stage 1 and begins enrolling patients in Stage 2. Please refer to the imaging manual and/or IRC charter for further details.

12.0 DATA HANDLING AND RECORD KEEPING

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 (WHO) Drug Dictionary.

12.1 eCRFs

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

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements 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, contract research organization (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 designee) 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 the 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 designee) will be permitted to review the patient'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, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient'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 for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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.

13.1.1 Analysis Sets

The analysis sets will include the following:

Safety analysis set: Patients who have received at least 1 dose, even if incomplete, of study drug will be used for all safety analyses and for some efficacy analyses.

PK analysis set: Patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include all DLT-evaluable patients as specified in Section 8.3. The DLT-evaluable population will be used to inform RP2D/MTD selection.

Response-evaluable analysis set: Patients who have received at least 1 dose of study drug, have sites of measurable disease at baseline, and have undergone 1 postbaseline disease assessment or were discontinued due to symptomatic deterioration or death before a postbaseline evaluation happens, will be used for analyses of response.

Phase 2 efficacy analysis set: All patients who received at least 1 dose of study drug in Phase 2 portion will be included in the Phase 2 efficacy analysis.

Pharmacodynamic analysis sets:

Pharmacodynamic analysis sets to assess target engagement of TAK-981 and SUMOylation pathway inhibition:

- Patients who have provided evaluable paired tumor biopsies (screening and postdose) will be included in the *tumor pharmacodynamic analysis dataset*.
- Patients who have provided evaluable blood samples (C1D1 predose sample and at least 1 postdose sample) will be included in the *blood pharmacodynamic analysis dataset*.

For exploratory biomarkers, the following may be included in the analysis sets:

- Patients who have provided evaluable plasma samples (C1D1 predose sample and at least 1 postdose sample) may be included in the *plasma chemokine/cytokine pharmacodynamic analysis dataset*.
- Patients who have provided evaluable paired tumor biopsies (screening and postdose) may be included in the *tumor immunophenotyping and/or tumor gene expression pharmacodynamic analysis dataset*.

- Patients who have provided evaluable blood samples (C1D1 predose sample and at least 1 postdose sample) may be included in the *blood/PBMCs immunophenotyping and/or blood gene expression pharmacodynamic analysis dataset*.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. 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 as needed.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

Phase 1b:

Efficacy is not the primary objective for this study in the Phase 1b portion. The efficacy analysis will mainly focus on the Phase 2 portion of this study.

In the Phase 1b portion of this study, efficacy parameters such as ORR, DCR, DRR, DOR, TTR, TTP, and PFS, may be summarized as appropriate. Disease response will be categorized and presented in listings.

Phase 2:

The primary endpoint for Phase 2 portion is ORR (CR + PR) as defined by the investigator according to RECIST, Version 1.1.

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study according to RECIST, Version 1.1.

The primary efficacy analysis will be based on the Phase 2 efficacy analysis set.

Estimates of the ORR (CR + PR) will be presented with 2-sided 95% exact binomial confidence intervals. Additional confidence intervals may also be provided as appropriate.

13.1.3.2 Secondary Efficacy Analysis

Secondary efficacy endpoints include DCR, DRR, DOR, TTR, TTP, PFS, and OS (Phase 2 only) as assessed by the investigator according to both RECIST, Version 1.1 and iRECIST; and ORR as assessed by the investigator according to iRECIST.

DCR is defined as the proportion of patients who achieve stable disease (SD) or better (CR+PR+SD determined by the investigator) during the study.

DRR is defined as the rate of objective responses (CR and PR as determined by the investigator) maintained for at least 6 months initiating at any time within 12 months of commencing therapy.

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 the last response assessment that is SD or better.

TTR is defined as the time from the date of the first dose to the date of the first documentation of objective tumor response (CR and PR as determined by the investigator).

TTP is defined as the time from the date of the first dose to the date of the first documentation of PD as defined by standard disease criteria.

PFS is defined as the time from the date of the first dose administration to the date of first documentation of PD or death due to any cause, whichever occurs first. PD will be determined by the investigator for both RECIST, Version 1.1 and iRECIST. Patients without documentation of PD 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 the first dose administration to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study according to iRECIST.

Estimates of ORR, DCR, and DRR will be presented with 2-sided 95% exact binomial confidence intervals. Additional confidence intervals may also be provided as appropriate.

PFS, OS, DOR, and TTP will be analyzed using Kaplan-Meier method for the Phase 2 efficacy analysis set. TTR will be summarized for responders.

All efficacy endpoints may be analyzed for the overall study population as appropriate.

13.1.4 PK Analysis

The PK of TAK-981 will be characterized in this study on Day 1 and Day 8 of the dose escalation phase of the study. PK of pembrolizumab will not be characterized.

PK parameters for TAK-981 will be estimated using noncompartmental methods with Phoenix WinNonlin software. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be estimated, as permitted by data:

- Maximum observed concentration (C_{max}).
- Time of first occurrence of C_{max} (t_{max}).
- AUC_{∞}.
- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Terminal disposition phase half-life ($t_{1/2z}$).
- Clearance (CL).

- V_{ss}.

PK parameters will be summarized using descriptive statistics. Individual TAK-981 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. The above parameters will not be estimated for the sparse PK samples collected during the Phase 2 portion of study.

The serial and sparse PK data collected in this study are intended to contribute to future population PK analyses of TAK-981. These population PK analyses may include data collected in other TAK-981 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

13.1.5 Pharmacodynamic Analysis

The analysis of tumor and blood biomarker profiles for each dose and timepoint tested will be tabulated. When possible, the dynamic range for each biomarker and fold change will be determined to better understand the TAK-981 biological activity range and duration of pharmacodynamic effects, and to help determine the PAD/RP2D for the TAK-981/pembrolizumab combination. In addition, candidate response biomarkers will be evaluated.

13.1.6 PK/Pharmacodynamic Analysis

Data permitting, the PK and pharmacodynamic data collected in this study will be analyzed to understand the exposure-response relationship for TAK-981 in combination with pembrolizumab. Such analyses may be performed on an ongoing basis to assess the appropriateness of dose and dosing schedule of TAK-981 in combination with pembrolizumab and for determination of PAD.

To determine the appropriateness of the PAD/MTD and schedule, a totality of evidence approach will be used that will integrate all available data from the dose escalation and the Phase 2 portions of the study, including:

1. Multicycle safety/tolerability of TAK-981 in combination with pembrolizumab.
2. Single- and multiple-dose PK of TAK-981.
3. Single- and multiple-dose pharmacodynamic biomarkers of TAK-981 (in circulation and tumor when available) including target engagement (adduct formation), SUMO2/3 inhibition, Type 1 IFN response gene signature, cytokines/chemokines in circulation, and blood immunophenotyping.
4. Antitumor response with TAK-981 in combination with pembrolizumab administration.
5. Relative dose intensity.

Dose-exposure-response relationships will be explored to describe the PK-safety, PK-pharmacodynamics, and PK-antitumor response relationships of TAK-981, and the results of

such quantitative pharmacology analyses will be used to inform selection of the RP2D/dosing schedule of TAK-981 in combination with pembrolizumab.

In addition, PK-pharmacodynamic data collected in the study during dose escalation may be used to inform the quantitative systems pharmacology model that may be used to further refine the dose/dosing schedule for TAK-981. Furthermore, the PK-pharmacodynamic data collected in this study may be pooled with similar data from other clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and quantitative systems pharmacology modeling may not be presented in the clinical study report for this study but will be presented in a separate report.

13.1.7 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs.
- SAEs (related and regardless of relationship).
- AESIs
- TEAE leading to study drug modification and discontinuation.

The incidence of DLTs will be tabulated using the DLT-evaluable analysis set.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized using a shift table.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as

scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of TAK-981 in combination with pembrolizumab.

All concomitant medications collected from the first dose of study drug throughout the study period will be classified to preferred terms according to the World Health Organization drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-981 in combination with pembrolizumab.

13.2 Interim Analysis and Criteria for Early Termination

Although no formal interim analysis is planned, investigators and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort in the dose escalation phase (see Section 8.4).

During the Phase 2 part of the study, if any arms in Cohorts A to F shows an ORR below the futility boundary in the first stage, then the enrollment in that specific arm will be stopped (see Section 13.3).

13.3 Determination of Sample Size

It is anticipated that approximately 231 patients will be enrolled in this study, including the Phase 1b portion dose escalation phase and the Phase 2 preliminary evaluation of the antitumor efficacy of the combination at the select Phase 2 doses in patients with select advanced or metastatic solid tumors, such as NSCLC, cervical, MSS-CRC, and melanoma.

Dose Escalation Phase (Phase 1b):

The BOIN design will be implemented for the dose escalation phase. It is estimated that up to approximately 32 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981 (ie, Days 1, 4, 8, and 11 or Days 1 and 8 in 21-day cycles).

Efficacy Evaluation Phase (Phase 2):

After select Phase 2 doses are identified, up to approximately 199 response-evaluable patients with select indications and dose levels in 8 cohorts will be enrolled in the Phase 2 study to evaluate the antitumor efficacy of the combination of TAK-981 and pembrolizumab.

The primary endpoint for the Phase 2 portion is ORR (CR + PR) as assessed by the investigator according to RECIST, Version 1.1. The sample size consideration for disease-specific patient populations is an adaptive design based on Simon's 2-stage design for a single proportion (Lin and Shih 2004) with the following hypotheses of ORR.

For Cohorts A through C and Cohort E, the hypotheses for Stage 1 are:

H_0: ORR $< p_0$ where $p_0 = 15\%$

H_1: ORR $\geq p_0$ where $p_0 = 15\%$

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted at Stage 1), further patients will be enrolled based on the number of responders in Stage 1 and their data will be collected in the second stage.

The hypotheses for the cohorts above (Cohorts A-C, and E) at the end of Stage 2 for a low desirable ORR, p_1, are:

a) H_1 is accepted at Stage 1, and

b) H_0: ORR $\leq p_1$ where $p_1 = 35\%$

H_1: ORR $> p_1$ where $p_1 = 35\%$

The hypotheses for the cohorts above (Cohorts A-C, and E) at the end of Stage 2 for a high desirable response, p_2, are:

a) H_1 is accepted at Stage 1, and

b) H_0: ORR $\leq p_2$ where $p_2 = 45\%$

H_1: ORR $> p_2$ where $p_2 = 45\%$

In order to have higher power for detecting more improvement of the new combination therapy (p_2 vs p_0) assuming a power of 90% for high-desirable response, 80% for low desirable-response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage.

Table 13.a Sample Size for Each Cohort and Each Stage (Cohorts A-C, and E)

	Stage		Total Number of Patients in Each Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of Stage 1				
Number of patients	9	23	23	0.1/80%
Number of responses [a]	≥2 and ≤5	≥6		
High response at the end of Stage 1				
Number of patients	9	15	15	0.1/90%
Number of responses	≥6	≥7		

[a] Number of patients needed to respond in order to continue into Stage 2 or have a positive result at the end of Stage 2.

[b] Maximum number of patients required for each cohort and number of responders that should be presented at the end of Stage 2 in order to claim treatment effect.

For Cohort D (Figure 6.a), the hypotheses for Stage 1 are the following:

H_0: ORR $< p_0$ where $p_0 = 45\%$

H_1: ORR $\geq p_0$ where $p_0 = 45\%$

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted) at Stage 1, additional patients will be enrolled based on the number of responders in Stage 1 and their data will be collected in the second stage.

The hypotheses for Cohort D at the end of Stage 2 for a low desirable ORR, p1, are the following:

a) H_1 is accepted at Stage 1, and

b) H_0: ORR $\leq p_1$ where $p_1 = 65\%$

H_1: ORR $> p_1$ where $p_1 = 65\%$

The hypotheses for Cohort D at the end of Stage 2 for a high desirable response, p2, are the following:

a) H_1 is accepted at Stage 1, and

b) H_0: ORR $\leq p_2$ where $p_2 = 75\%$

H_1: ORR $> p_2$ where $p_2 = 75\%$

Similarly, for Cohort D, assuming a power of 90% for high desirable response and 80% for low desirable response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 13.b).

Table 13.b Sample Size for Each Cohort and Each Stage (Cohort D)

	Stage		Total Number of Patients in Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of Stage 1				
Number of patients	11	36	36	0.1/80%
Number of responses [a]	≥6 and ≤9	≥20		
High response at the end of Stage 2				
Number of patients	11	19	19	0.1/90%
Number of responses	≥10	≥14		

[a] Number of patients needed to respond to continue into Stage 2 or have a positive result at the end of Stage 2.

[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of Stage 2 in order to claim treatment effect.

For CPI refractory NSCLC cohort (Cohort F with 2 dose levels: 90 mg BIW & 120 mg QW), Simon's 2-stage design (Simon 1989) will be used for sample size calculation. The null hypothesis that the true response rate is ($p_0 \leq 5\%$) will be tested against a 1-sided alternative.

In the first stage, 10 evaluable patients will be accrued. If there are 0 responses observed in these 10 patients, the cohort will be stopped; otherwise, 14 additional patients will be accrued for a total of 24.

The null hypothesis will be rejected if 4 or more responses are observed in the total of 24 patients. This design yields power of 85% and 1-sided Type I error rate of 0.05 when the true response rate is ≥25%.

Table 13.c CPI Primary Refractory: Sample Size for Each Cohort and Each Stage (Cohort F: 90 mg BIW & 120 QW)

	Stage		Total Number of Patients in Each Cohort	One-Sided Alpha Level/Power
	Stage I	Stage II [b]		
Response at the end of stage I				
Number of patients	10	24	24	0.05/85%
Number of responses a	≥1	≥4		

BWI: twice weekly; CPI: checkpoint inhibitor; QW: once weekly.

[a] Number of patients needed to respond to continue into Stage II or have a positive result at the end of Stage II.

[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of Stage II to claim treatment effect.

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. If monitors are not allowed to visit sites for data verification due to pandemic (eg, COVID-19), remote electronic medical records access visits may be made (where allowed by sites). 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, patient medical records, informed consent documentation, documentation of patient 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 patient'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 patient, 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 patient 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.

The investigator should document all protocol deviations.

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], 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 B. 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 state and 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, patient 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 patient 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/notify site 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 drug/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 patients, 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 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, patient 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 patient authorization form. The ICF, patient authorization form (if

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

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. 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 patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient'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 patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient enters into the study. The patient or the patient'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 patient authorization (if applicable) at the time of consent and before the patient 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, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient'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 patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient'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 patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient'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 patient'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 patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient'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 email/phone or other methods preferred by callers requesting trial information. Once patients 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 patient 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.

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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient 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 patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

2009. ICH Harmonised Tripartite Guideline. Nonclinical evaluation for anticancer pharmaceuticals; Guidance for Industry, S9.: International Conference on Harmonisation.

Adams, S. 2009. Toll-like receptor agonists in cancer therapy. *Immunotherapy,* 1(6), 949-64.

Brahmer, J., Reckamp, K. L., Baas, P., Crino, L., Eberhardt, W. E., Poddubskaya, E., et al. 2015. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med,* 373(2), 123-35.

Broz, M. L., Binnewies, M., Boldajipour, B., Nelson, A. E., Pollack, J. L., Erle, D. J., et al. 2014. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell,* 26(5), 638-52.

Chen, D. S. and Mellman, I. 2013. Oncology meets immunology: the cancer-immunity cycle. *Immunity,* 39(1), 1-10.

Chung, H. C., Ros, W., Delord, J. P., Perets, R., Italiano, A., Shapira-Frommer, R., et al. 2019. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol,* 37(17), 1470-8.

Cockcroft, D. W. and Gault, M. H. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron,* 16(1), 31-41.

Crowl, J. T. and Stetson, D. B. 2018. SUMO2 and SUMO3 redundantly prevent a noncanonical type I interferon response. *Proc Natl Acad Sci U S A,* 115(26), 6798-803.

Curtsinger, J. M., Valenzuela, J. O., Agarwal, P., Lins, D. and Mescher, M. F. 2005. Type I IFNs provide a third signal to CD8 T cells to stimulate clonal expansion and differentiation. *J Immunol,* 174(8), 4465-9.

Decque, A., Joffre, O., Magalhaes, J. G., Cossec, J. C., Blecher-Gonen, R., Lapaquette, P., et al. 2016. Sumoylation coordinates the repression of inflammatory and anti-viral gene-expression programs during innate sensing. *Nat Immunol,* 17(2), 140-9.

Diamond, M. S., Kinder, M., Matsushita, H., Mashayekhi, M., Dunn, G. P., Archambault, J. M., et al. 2011. Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J Exp Med,* 208(10), 1989-2003.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., et al. 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer,* 45(2), 228-47.

Fuertes, M. B., Kacha, A. K., Kline, J., Woo, S. R., Kranz, D. M., Murphy, K. M., et al. 2011. Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8{alpha}+ dendritic cells. *J Exp Med,* 208(10), 2005-16.

Gadgeel, S., Garassino, M. C., Esteban, E., Speranza, G., Felip, E., Hochmair, M. J., et al. 2019. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. *J Clin Oncol,* 37(no. 15_suppl), 9013.

Gandhi, L., Rodriguez-Abreu, D., Gadgeel, S., Esteban, E., Felip, E., De Angelis, F., et al. 2018. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med,* 378(22), 2078-92.

Gareau, J. R. and Lima, C. D. 2010. The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nat Rev Mol Cell Biol,* 11(12), 861-71.

Garon, E. B., Ciuleanu, T. E., Arrieta, O., Prabhash, K., Syrigos, K. N., Goksel, T., et al. 2014. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet,* 384(9944), 665-73.

Geiss-Friedlander, R. and Melchior, F. 2007. Concepts in sumoylation: a decade on. *Nat Rev Mol Cell Biol,* 8(12), 947-56.

Gresser, I., Guy-Grand, D., Maury, C. and Maunoury, M. T. 1981. Interferon induces peripheral lymphadenopathy in mice. *J Immunol,* 127(4), 1569-75.

Hansen, A. R., Cook, N., Amir, E., Siu, L. L. and Abdul Razak, A. R. 2017. Determinants of the recommended phase 2 dose of molecular targeted agents. *Cancer,* 123(8), 1409-15.

He, X., Riceberg, J., Soucy, T., Koenig, E., Minissale, J., Gallery, G., et al. 2017. Probing the roles of SUMOylation in cancer cell biology by using a selective SAE inhibitor. *Nature Chemical Biology,* 13, 1164-73.

Herbst, R. S., Baas, P., Kim, D. W., Felip, E., Perez-Gracia, J. L., Han, J. Y., et al. 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet,* 387(10027), 1540-50.

Hodi, F. S., O'Day, S. J., McDermott, D. F., Weber, R. W., Sosman, J. A., Haanen, J. B., et al. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med,* 363(8), 711-23.

Horn, L., Spigel, D. R., Vokes, E. E., Holgado, E., Ready, N., Steins, M., et al. 2017. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: Two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol,* 35(35), 3924-33.

Jenkins, R. W., Barbie, D. A. and Flaherty, K. T. 2018. Mechanisms of resistance to immune checkpoint inhibitors. *Br J Cancer,* 118(1), 9-16.

Kamphuis, E., Junt, T., Waibler, Z., Forster, R. and Kalinke, U. 2006. Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. *Blood,* 108(10), 3253-61.

Kantoff, P., Higano, C., Shore, N., Berger, E., Small, E., Penson, D., et al. 2010. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *New England Journal of Medicine,* 363(5), 411-22.

Keytruda (pembrolizumab) Injection for Intravenous Use 2023. Full Prescribing Information. Merck Sharp & Dohme LLC.

Le, D. T., Uram, J. N., Wang, H., Bartlett, B. R., Kemberling, H., Eyring, A. D., et al. 2015. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *New England Journal of Medicine,* 372(26), 2509-20.

Lee, C. K., Rao, D. T., Gertner, R., Gimeno, R., Frey, A. B. and Levy, D. E. 2000. Distinct requirements for IFNs and STAT1 in NK cell function. *J Immunol,* 165(7), 3571-7.

Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., et al. 2019. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant,* 25(4), 625-38.

Lin, Y. and Shih, W. J. 2004. Adaptive two-stage designs for single-arm phase IIA cancer clinical trials. *Biometrics,* 60(2), 482-90.

Long, H. J., 3rd, Bundy, B. N., Grendys, E. C., Jr., Benda, J. A., McMeekin, D. S., Sorosky, J., et al. 2005. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol,* 23(21), 4626-33.

Longoria, T. C. and Tewari, K. S. 2016. Evaluation of the pharmacokinetics and metabolism of pembrolizumab in the treatment of melanoma. *Expert Opin Drug Metab Toxicol,* 12(10), 1247-53.

Lucas, M., Schachterle, W., Oberle, K., Aichele, P. and Diefenbach, A. 2007. Dendritic cells prime natural killer cells by trans-presenting interleukin 15. *Immunity,* 26(4), 503-17.

Marrack, P., Kappler, J. and Mitchell, T. 1999. Type I interferons keep activated T cells alive. *J Exp Med,* 189(3), 521-30.

Mayer, R. J., Van Cutsem, E., Falcone, A., Yoshino, T., Garcia-Carbonero, R., Mizunuma, N., et al. 2015. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *New England Journal of Medicine,* 372(20), 1909-19.

Minn, A. J. and Wherry, E. J. 2016. Combination Cancer Therapies with Immune Checkpoint Blockade: Convergence on Interferon Signaling. *Cell,* 165(2), 272-5.

Monk, B. J., Sill, M. W., McMeekin, D. S., Cohn, D. E., Ramondetta, L. M., Boardman, C. H., et al. 2009. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol,* 27(28), 4649-55.

Moore, D. H., Blessing, J. A., McQuellon, R. P., Thaler, H. T., Cella, D., Benda, J., et al. 2004. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol,* 22(15), 3113-9.

NCI 2017. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Neelapu, S. S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F. L., et al. 2018. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol,* 15(1), 47-62.

O'Neil, B. H., Wallmark, J. M., Lorente, D., Elez, E., Raimbourg, J., Gomez-Roca, C., et al. 2017. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. *PLoS One* [Online], 12(12). doi:10.1371/journal.pone.0189848.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology,* 5(6), 649-55.

Overman, M. J., Lonardi, S., Wong, K. Y. M., Lenz, H. J., Gelsomino, F., Aglietta, M., et al. 2018. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol,* 36(8), 773-9.

Overman, M. J., McDermott, R., Leach, J. L., Lonardi, S., Lenz, H. J., Morse, M. A., et al. 2017. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high

colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol,* 18(9), 1182-91.

Plebani, M. 2021. Persistent viral RNA shedding in COVID-19: Caution, not fear. *EBioMedicine,* 64, 103234.

Qu, Y. M., Kang, E. M. and Cong, H. Y. 2020. Positive result of Sars-Cov-2 in sputum from a cured patient with COVID-19. *Travel Med Infect Dis,* 34, 101619.

Reck, M., Rodriguez-Abreu, D., Robinson, A. G., Hui, R., Csoszi, T., Fulop, A., et al. 2019. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol,* 37(7), 537-46.

Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., von Pawel, J., et al. 2017. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet,* 389(10066), 255-65.

Robert, C., Ribas, A., Schachter, J., Arance, A., Grob, J. J., Mortier, L., et al. 2019. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol,* 20(9), 1239-51.

Robert, C., Schachter, J., Long, G. V., Arance, A., Grob, J. J., Mortier, L., et al. 2015. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med,* 372(26), 2521-32.

Schachter, J., Ribas, A., Long, G. V., Arance, A., Grob, J. J., Mortier, L., et al. 2017. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet,* 390(10105), 1853-62.

Seeler, J. S. and Dejean, A. 2017. SUMO and the robustness of cancer. *Nat Rev Cancer,* 17(3), 184-97.

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L. H., Mandrekar, S., et al. 2017. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncology,* 18(3), e143-e52.

Shah, M., Rahman, A., Theoret, M. R. and Pazdur, R. 2021. The drug-dosing conundrum in oncology - when less is more. *N Engl J Med,* 385(16), 1445-7.

Sharma, P., Hu-Lieskovan, S., Wargo, J. A. and Ribas, A. 2017. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell,* 168(4), 707-23.

Shiow, L. R., Rosen, D. B., Brdickova, N., Xu, Y., An, J., Lanier, L. L., et al. 2006. CD69 acts downstream of interferon-alpha/beta to inhibit S1P1 and lymphocyte egress from lymphoid organs. *Nature,* 440(7083), 540-4.

Siegel, R., Ma, J., Zou, Z. and Jemal, A. 2014. Cancer statistics, 2014. *CA Cancer J Clin,* 64(1), 9-29.

Siegel, R. L., Miller, K. D. and Jemal, A. 2019. Cancer statistics, 2019. *CA Cancer J Clin,* 69(1), 7-34.

Siegel, R. L., Miller, K. D. and Jemal, A. 2020. Cancer statistics, 2020. *CA Cancer J Clin,* 70(1), 7-30.

Simon, R. 1989. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials,* 10(1), 1-10.

Thall, P. F. and Sung, H. G. 1998. Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Statistics in Medicine,* 17(14), 1563-80.

Van Cutsem, E., Tabernero, J., Lakomy, R., Prenen, H., Prausova, J., Macarulla, T., et al. 2012. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized

trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol,* 30(28), 3499-506.

West, H., McCleod, M., Hussein, M., Morabito, A., Rittmeyer, A., Conter, H. J., et al. 2019. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol,* 20(7), 924-37.

Woo, S. R., Fuertes, M. B., Corrales, L., Spranger, S., Furdyna, M. J., Leung, M. Y., et al. 2014. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. *Immunity,* 41(5), 830-42.

Yuan, Y., Hess, K. R., Hilsenbeck, S. G. and Gilbert, M. R. 2016. Bayesian optimal interval design: A simple and well-performing design for phase i oncology trials. *Clin Cancer Res,* 22(17), 4291-301.

Appendix A Schedule of Events

Table 1.a Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 1)

Procedure/Assessment	Screening [a]	Cycle 1 Days 1	2	4	8	9	11	15	Cycle 2 Days 1	4	8	11	15	Cycle 3 and Onward Days 1	4	8	11	15	EOT	30 and 90 (+10) Days After Last Dose	Survival Follow-up [b]
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics	X																				
Medical history [c]	X																				
Available tumor genomic/cytogenetic/mutational information [c]	X																				
Tumor PD-L1 status [c]	X																				
Physical examination [d]	X																				
Symptom-directed physical examination [e]									X					X					X	X	
Height	X																				
Weight	X	X							X					X					X	X	
ECOG performance status [e]	X	X							X					X					X	X	
Vital signs [f]	X	X		X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X	
12-lead safety ECG [i]	X	X2			X2				X2		X2			X2					X		
Echocardiography/MUGA (LVEF) scan [j]	X													X					X		
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.																				
Adverse event reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug or start of a new systemic treatment.																				
	SAEs will be reported from the signing of the ICF through 30 days after the last dose of study drug or any moment after EOT for related SAEs. **AESIs** will be reported from the C1D1 through 90 days after the last dose of study drug or any moment after EOT.																				
TAK-981 administration [k]		X		X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]			
Pembrolizumab administration [k]		X							X					X							
Samples/Laboratory Assessments																					
Pregnancy test, β-HCG (urine or serum) [l]	X	X							X					X					X		
Hematology/chemistry [m]	X	X		X [g]	X		X [g]	X [h]	X					X					X		
Coagulation [m]	X													X					X		
Urinalysis [m, n]	X	X							X					X					X		
Tumor prognostic markers [o]		X							X					X							

Table 1.a Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 1)

Procedure/Assessment	Screening [a]	Cycle 1 Days 1	2	4	8	9	11	15	Cycle 2 Days 1	4	8	11	15	Cycle 3 and Onward Days 1	4	8	11	15	EOT	30 and 90 (+10) Days After Last Dose	Survival Follow-up [b]
Immunosafety markers (hormones) [p]	X													X					X		
Disease assessment [q, r]	X																				
PK samples	Refer to Table 2.a (Phase 1b).																				
Biomarker samples	Refer to Table 3.a (Phase 1b).																				

AESI: adverse event of special interest; COVID-19: coronavirus disease 2019; CT: computed tomography; CxDx: Cycle x, Day x; ECG: electrocardiogram, ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; FDG: fluorodeoxyglucose; HCG: human chorionic gonadotropin; ICF: informed consent form; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multiple-gated acquisition; PD: progressive disease; PD-L1: programmed cell death protein 1 ligand; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event.

Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. For individual instances where assessments or procedures are not able to be performed as defined in the protocol, the reasons for failing to perform those should be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified visit, assessment, or procedure). If a treatment visit is delayed, associated tests and procedures should also be delayed. If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Signed informed consent must be obtained before performing any protocol-specific procedure.

[b] The survival status of patients who permanently discontinue all study treatment for reasons specified in Section 9.7, with the exception of death, or withdrawal by the patient, or PD by iRECIST, will be assessed through medical charts or by telephone following the last administration of the study drugs.

[c] Any available pathology/cytogenetic/mutational information for all patients should be reported in the eCRF. Tumor PD-L1 status is required from all patients in Phase 2. For more information, see Protocol, Section 9.4.3.

[d] Complete physical exam at screening. If screening is performed more than 4 days before C1D1, the exam should be performed again before dosing.

[e] The symptom-directed physical examination and ECOG will be conducted within 3 days before dosing on Day 1 of each treatment cycle and at the EOT/early termination 30 and 90 days after last dose visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[f] Perform vital signs measurement before and after dosing. Blood pressure, heart rate, and temperature will be measured immediately before the start of the infusion and at the end of the infusion of each study drug. Blood pressure should be determined after the patient has been resting for 5 minutes.

[g] For patients enrolled in the dosing schedule of TAK-981 on Days 1, 4, 8, and 11 every 21 days.

[h] For patients enrolled in the dosing schedule of TAK-981 on Days 1, 8, and 15 every 21 days.

[i] Single safety ECGs will be collected at screening, pre-TAK-981 dose and post-TAK-981 EOI (+1-h window) on Days 1 and 8 of Cycles 1 and Cycle 2. From Cycle 3 onwards, pre-TAK-981 dose and post-TAK-981 EOI (+1-h window) ECGs will be collected on Day 1 of every other cycle. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient rested for 5 minutes.

[j] The MUGA (LVEF) scan should be performed at screening to ensure patient eligibility. Echocardiographic estimate of the left ventricular ejection fraction can be measured as an alternative to MUGA scans. From Cycle 3 onwards, MUGA (LVEF) scan will be repeated every 3 cycles and at EOT. From Cycle 3 onwards, a ±7-day window is allowed for this test.

[k] On days on which the infusion of TAK-981 and pembrolizumab coincide, TAK-981 is administered first. At least 30 minutes should elapse between the completion of the first study drug and the initiation of the second study drug. Patients with clinical benefit can be changed to a less frequent schedule if the investigator, in agreement with the sponsor, considers that continuing with the intensive schedule would negatively impact the patient's well-being. Dose administration of TAK-981 and pembrolizumab should be performed on schedule; however, a dose delay of up to 3 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor. If a treatment visit is delayed, associated tests and procedures should also be delayed.

[l] A serum or urine choriogonadotropin beta (β-hCG) pregnancy test will be performed only for women of childbearing potential during screening, again at C1D1 (baseline) if the screening test was performed more than 72 hours before the first dose of any study drug. From Cycle 2 onwards, serum or urine pregnancy test samples should be collected on Day 1 or within 72 hours prior to Day 1 of each subsequent cycle. The results must be negative within 72 hours before TAK-981 is administered or as otherwise required by local regulations.

[m] Hematology, chemistry, coagulation, and urinalysis may be taken up to 3 days prior to the Day 1 visit. Day 4, 8, 11, 15 hematology and chemistry assessments are to be performed on dosing days depending on treatment schedule (these assessments may be discontinued during Phase 2).

[n] Urinalysis includes tests for pH, protein, glucose, ketones, urobilinogen, bilirubin, leukocytes, erythrocytes, nitrites, and density. In the event significant abnormalities are detected in proteins, leukocytes or blood, a microscopic analysis of urine sediment should be performed. From C1 onwards, urine tests will be taken only on Day 1 of each cycle and at EOT.

[o] Tumor prognostic markers (CEA and CA 19-9 in colon cancer patients, CA 15-3 and CA 125 in cervical cancer patients, and only in Phase 2) may be performed up to 3 days prior to D1 visit. For specifics, see Section 9.4.12.1.

[p] Immunosafety determinations include thyroid-stimulating hormone, free thyroxine, and adrenocorticotropic hormone measured in blood at screening and repeated at the beginning of each cycle from C3 until C6, every other cycle afterwards, and at the EOT.

[q] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis must be acquired at screening. Subsequent assessments must be performed by using the same imaging modality (contrast-enhanced CT or MRI).

[r] Contrast-enhanced CT or MRI and FDG-PET should be performed every 2 months from C1D1 (62 days ± 7 days), or more frequently if clinically indicated. After 6 months, imaging frequency should be reduced to every 3 months (93 days ±7 days) until occurrence of progression of disease. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (ie, administration of TAK-981 or pembrolizumab). The same imaging modality (contrast-enhanced CT or MRI, and FDG-PET scan) should be used on a patient at the screening visit and throughout the study. Bone scans may be performed on patients as clinically indicated. Response will be determined according to RECIST, Version 1.1 criteria.

Table 1.b Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 2)

Procedure/Assessment	Screening [a]	Cycle 1 Days 1	2	4	8	9	11	Cycle 2 Days 1	4	8	11	Cycle 3 Days 1	4	8	11	Cycle 4 and Onwards Days 1	2	4	8	9	11	EOT	30 and 90 (+10) Days After Last Dose	Survival Follow-up [b]
Informed consent	X																							
Inclusion/exclusion criteria	X																							
Demographics	X																							
Medical history [c]	X																							
Available tumor genomic/cytogenetic/mutational information [c]	X																							
Tumor PD-L1 status [c]	X																							
Physical examination [d]	X																							
Symptom-directed physical examination [e]								X				X				X						X	X	
Height	X																							
Weight	X	X						X				X				X						X	X	
ECOG performance status [e]	X	X						X				X				X						X	X	
Vital signs [f]	X	X		X [g]	X		X [g]	X	X [g]	X	X [g]	X	X [g]	X	X [g]	X		X [g]	X		X [g]	X	X	
12-lead safety ECG [h]	X	X2			X2			X2		X2		X2										X		
Echocardiography/MUGA (LVEF) scan [i]	X											X										X		
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first																							
Adverse event reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug or start of a new systemic treatment																							
	SAEs will be reported from the signing of the ICF through 30 days after the last dose of study drug or any moment after EOT for related SAEs. **AESIs** will be reported from the C1D1 through 90 days after the last dose of study drug or any moment after EOT.																							
TAK-981 administration [j]		X		X [g]	X		X [g]	X	X [g]	X	X [g]	X	X [g]	X	X [g]	X		X [g]	X		X [g]			
Pembrolizumab administration [j]		X						X				X				X								
Samples/Laboratory Assessments																								
Pregnancy test, β-HCG (urine or serum) [k]	X	X						X				X				X						X		
Hematology/chemistry [l]	X	X		X [g]	X		X [g]	X		X		X		X		X			X			X		
Coagulation [l]	X											X				X						X		
Urinalysis [l,m]	X	X						X				X				X						X		

Table 1.b Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 2)

Procedure/Assessment	Screening [a]	Cycle 1 Days 1	2	4	8	9	11	Cycle 2 Days 1	4	8	11	Cycle 3 Days 1	4	8	11	Cycle 4 and Onwards Days 1	2	4	8	9	11	EOT	30 and 90 (+10) Days After Last Dose	Survival Follow-up [b]
Tumor prognostic markers [n]		X						X				X				X								
Immunosafety markers (hormones) [o]	X											X				X						X		
Disease assessment [p,q]	X																							
PK samples		Refer to Table 2.b (Phase 2)														Refer to Table 2.b (Phase 2)								
Biomarker samples	Refer to Table 3.b (Phase 2)																							

AESI: adverse event of special interest; COVID-19: coronavirus disease 2019; CT: computed tomography; CxDx: Cycle x, Day x; ECG: electrocardiogram, ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; FDG: fluorodeoxyglucose; HCG: human chorionic gonadotropin; ICF: informed consent form; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multiple-gated acquisition; PD-L1: programmed cell death protein 1 ligand; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event.

Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. For individual instances where assessments or procedures are not able to be performed as defined in the protocol, the reasons for failing to perform those should be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified visit, assessment, or procedure). If a treatment visit is delayed, associated tests and procedures should also be delayed. If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.

EOT procedures to be completed by all patients at the time of study drug discontinuation. For patients who discontinue, the EOT visit should be performed instead of the scheduled trial visit at time of discontinuation.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Signed informed consent must be obtained before performing any protocol-specific procedure.

[b] The survival status of patients in Phase 2 who permanently discontinue all study treatment for reasons specified in Section 9.7, with the exception of death, or withdrawal by the patient, will be assessed through medical charts or by telephone following the last administration of the study drugs.

[c] Any available pathology/cytogenetic/mutational information for all patients should be reported in the eCRF. Tumor PD-L1 status is required from all patients in Phase 2. For more information, see Protocol, Section 9.4.3.

[d] Complete physical exam at screening. If screening is performed more than 4 days before C1D1, the exam should be performed again before dosing.

[e] The symptom-directed physical examination and ECOG will be conducted within 3 days before dosing on Day 1 of each treatment cycle and at the EOT/early termination 30 and 90 days after last dose visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[f] Perform vital signs measurement before and after dosing. Blood pressure, heart rate, and temperature will be measured immediately before the start of the infusion and at the end of the infusion of each study drug. Blood pressure should be determined after the patient has been resting for 5 minutes.

[g] For patients enrolled in the dosing schedule of TAK-981 on Days 1, 4, 8, and 11 every 21 days.

[h] Single safety ECGs will be collected at screening, pre-TAK-981 dose and post-TAK-981 EOI (+1-h window) on Days 1 and 8 of Cycles 1 and Cycle 2. From Cycle 3 onwards, pre-TAK-981 dose and post-TAK-981 EOI (+1-h window) ECGs will be collected on Day 1 of every other cycle. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient rested for 5 minutes.

[i] The MUGA (LVEF) scan should be performed at screening to ensure patient eligibility. Echocardiographic estimate of the left ventricular ejection fraction can be measured as an alternative to MUGA scans. From Cycle 3 onwards, MUGA (LVEF) scan will be repeated every 3 cycles and at EOT. From Cycle 3 onwards, a ±7-day window is allowed for this test.

[j] On days on which the infusion of TAK-981 and pembrolizumab coincide, TAK-981 is administered first. At least 30 minutes should elapse between the completion of the first study drug and the initiation of the second study drug. Patients with clinical benefit can be changed to a less frequent schedule if the investigator, in agreement with the sponsor, considers that continuing with the intensive schedule would negatively impact the patient's well-being. Dose administration of TAK-981 and pembrolizumab should be performed on schedule; however, a dose delay of up to 3 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor. If a treatment visit is delayed, associated tests and procedures should also be delayed.

[k] A serum or urine choriogonadotropin beta (β-hCG) pregnancy test will be performed only for women of childbearing potential during screening, again at C1D1 (baseline) if the screening test was performed more than 72 hours before the first dose of any study drug. From Cycle 2 onwards, serum or urine pregnancy test samples should be collected on Day 1 or within 72 hours prior to Day 1 of each subsequent cycle. The results must be negative within 72 hours before TAK-981 is administered or as otherwise required by local regulations.

[l] Hematology, chemistry, coagulation, and urinalysis may be taken up to 3 days before the Day 1 visit. Hematology and chemistry assessments on Days 4, 8, and 11 (Cycle 1) and Days 1 and 8 (Cycle 2 and onwards) are to be performed on dosing days depending on treatment schedule (these assessments may be discontinued during Phase 2).

[m] Urinalysis includes tests for pH, protein, glucose, ketones, urobilinogen, bilirubin, leukocytes, erythrocytes, nitrites, and density. In the event significant abnormalities are detected in proteins, leukocytes or blood, a microscopic analysis of urine sediment should be performed. From C1 onwards, urine tests will be taken only on Day 1 of each cycle and at EOT.

[n] Tumor prognostic markers (CEA and CA 19-9 in colon cancer patients, CA 15-3 and CA 125 in cervical cancer patients, and only in Phase 2) may be performed up to 3 days prior to D1 visit. For specifics, see Section 9.4.12.1.

[o] Immunosafety determinations include thyroid-stimulating hormone (TSH), free thyroxine (FT4), adrenocorticotropic hormone (ACTH) measured in blood at screening and repeated at the beginning of each cycle from C3 until C6, every other cycle afterwards, and at the EOT.

[p] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis must be acquired at screening or within 28 days from C1D1. Subsequent assessments must be performed by using the same imaging modality (contrast-enhanced CT or MRI).

[q] Contrast-enhanced CT or MRI and FDG-PET should be performed every 2 months from C1D1 (62 days ± 7 days), or more frequently if clinically indicated. After 6 months, imaging frequency should be reduced to every 3 months (93 days ±7 days) until occurrence of progression of disease. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (ie, administration of TAK-981 or pembrolizumab). The same imaging modality (contrast-enhanced CT or MRI, and FDG-PET scan) should be used on a patient at the screening visit and throughout the study. Bone scans may be performed on patients as clinically indicated. Response will be determined according to RECIST, Version 1.1 criteria.

Table 2.a Plasma PK Sampling Schedule During Phase 1b

	Cycle 1				Cycle 2	
	Day 1	Day 4	Day 8	Day 11	Day 1	Day 8
	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)
Pre-TAK-981 dose (within 1 h before the start of infusion)	X		X			
End of TAK-981 infusion (±10 min)	X	X [a]	X	X [a]	X	X
2 h after end of TAK-981 infusion (±30 min)	X		X		X	X
4 h after end of TAK-981 infusion (±30 min)	X		X			
6 h after end of TAK-981 infusion (±30 min)	X		X			
24 h after end of TAK-981 infusion (±60 min)	X		X			
Total time points/samples	6	1	6	1	2	2

h: hour; PK: pharmacokinetic.

[a] For patients enrolled in the dosing schedule of TAK-981 on Day 1, or Days 1 and 8, or Days 1, 8, and 15 every 21 days, this test or procedure may not be performed.

Table 2.b Plasma PK Sampling Schedule During Phase 2

	Cycle 1		Cycle 2	
	Day 1	Day 8	Day 1	Day 8
	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)
Pre-TAK-981 dose (within 1 h before the start of infusion)	X	X	X	X
End of TAK-981 infusion (±10 min)	X	X	X	X
1-4 h after end of TAK-981 infusion (±30 min)	X	X	X	X
24 h after end of TAK-981 infusion (±3 h)	X	X		
Total time points/samples	4	4	3	3

h: hour; PK: pharmacokinetic.

Table 3.a Biomarker Sample Collection During Phase 1b

		C1D1					C1D8					C2D1	C2D8				C3D1, C6D1, C9D1	C3D8, C6D8, C9D8
			1 h	4 h	6-8 h	24 h		1 h	4 h	6-8 h	24 h			1 h	4 h	6-8 h		
	Screening	Pre-dose	Post-EOI	Post-EOI	Post-EOI	Post-EOI	Pre-dose	Post-EOI	Post-EOI	Post-EOI	Post-EOI	Pre-dose	Pre-dose	Post-EOI	Post-EOI	Post-EOI	Pre-dose	Pre-dose
Window period			+20 min	±30 min		±60 min		+20 min	±30 min		±60 min			+20 min	±30 min			
Archival (banked) tumor tissue sample [a]	X																	
Fresh tumor tissue biopsy sample [b]	X															X		
Plasma sample for chemokine/cytokine analysis [c]		X			X	X	X			X	X		X			X	X	X
Blood cells for immunophenotyping [c]		X				X	X				X		X			X	X	X
PBMCs sample for immunophenotyping [c]		X				X	X				X		X					
Whole blood sample for adducts/conjugates		X	X	X	X		X	X	X	X			X	X	X	X		
Blood sample for RNA [c]		X			X	X	X			X	X		X			X	X	X
Serum sample for circulating biomarkers		X				X												
Blood sample for DNA		X																
Blood sample for cfDNA [c]		X					X					X					X	

aPTT: activated partial thromboplastin time; cfDNA: cell-free DNA; CxDx: Cycle x, Day x; EOI: end of infusion; INR: international normalized ratio; PBMC: peripheral blood mononuclear cell.

"Predose" and "Post-EOI" refers to predose and end of TAK-981 infusion, respectively.

[a] Archival (banked) tumor tissue sample collected within 12 months of study initiation will be collected when available from all patients.

[b] Screening and on-treatment biopsies are encouraged (but optional) for all patients in Phase 1b. The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of study drug. The on-treatment biopsy will be obtained post TAK-981 infusion on C2D8 (+7 days). The accessible lesion biopsy (screening and on-treatment) should not have been previously designated as the only target lesion for measurable disease or being located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible. Hematology and coagulation tests including platelet counts, INR and aPTT should be performed prior to a biopsy procedure being performed and the risk of bleeding associated with the procedure must be assessed by the investigator. On-treatment biopsy collection visit day may be changed should data emerging would be supportive of such change.

[c] A decision to stop collection of plasma samples for chemokine/cytokine analysis, blood cells and PBMCs samples for immunophenotyping, blood sample for RNA, and blood sample for cfDNA may take place should sufficient data be generated.

Table 3.b Biomarker Sample Collection During Phase 2

		C1D1		C1D8		C2D1	C2 Biopsy (C2D8 +7 days)		C3	C4D1		C4D8		C6, and C9
			24h		24h						24h		24h	
	Screening	Predose	Post-EOI	Predose	Post-EOI	Predose	Pre-Biopsy	Biopsy	Predose	Predose	Post-EOI	Predose	Post-EOI	Predose
Archival (banked) tumor tissue sample if available [a]	X													
Tumor biopsy [b]	X													
Fresh paired tumor tissue biopsy sample [c]	X							X						
Plasma sample for chemokine/cytokine analysis [d]		X	X	X	X	X	X			X	X	X	X	
Blood cells for immunophenotyping [d]		X	X	X	X	X	X		X	X	X	X	X	X
Blood sample for RNA [d]		X	X	X	X	X	X			X	X	X	X	
Blood sample for cfDNA [d]		X				X				X				X

aPTT: activated partial thromboplastin time; cfDNA: cell-free DNA; CxDx: Cycle x, Day x; EOI: end of infusion; INR: international normalized ratio.

"Predose" and "Post-EOI" refers to predose and end of TAK-981 infusion, respectively.

Samples will only be collected if on-treatment biopsies are collected.

[a] Archival (banked) tumor tissue sample collected within 12 months of study initiation will be collected when available from all patients.

[b] Pretreatment fresh tumor biopsy at screening can be replaced by a recent (≤12 months old) formalin-fixed, paraffin-embedded tumor specimen. For fresh tumor biopsies, the lesion must be accessible for a low-risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal space, or those obtained with endoscopic procedures beyond the stomach or bowel).

[c] Screening and on-treatment biopsies are encouraged (but optional) for all patients in the study. The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of study drug. The on-treatment biopsy will be obtained post TAK-981 infusion on C2D8 (+7 days). The accessible lesion biopsy (screening and on-treatment) should not have been previously designated as the only target lesion for measurable disease or being located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible. Hematology and coagulation tests including platelet counts, INR and aPTT should be performed prior to a biopsy procedure being performed and the risk of bleeding associated with the procedure must be assessed by the investigator. On-treatment biopsy collection visit day may be changed should data emerging would be supportive of such change.

[d] A decision to stop collection of plasma samples for cfDNA, chemokine/cytokine analysis, blood samples for immunophenotyping, and blood sample for RNA may take place should sufficient data be generated.

Appendix B 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 who 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 patients before 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 patients. 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 patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient'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 C 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 D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, 1982 (Oken et al. 1982).

ECOG: Eastern Cooperative Oncology Group.

Appendix E Drugs That Interact With the CYP3A Family of CYPs

Drugs listed below which are strong or moderate inducers or inhibitors of the CYP3A family of CYPs are prohibited as concomitant medications with TAK-981. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A activity. Appropriate medical judgment is required. Please contact the sponsor's medical monitor with any queries.

Drugs Inducing or Inhibiting CYP3A Metabolism That Are Prohibited Concomitant Medications With TAK-981

Strong CYP3A Inducers [a]	Strong CYP3A Inhibitors [b]
apalutamide carbamazepine enzalutamide mitotane phenytoin rifampin St John's Wort	boceprevir clarithromycin cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice idelalisib indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir nefazodone nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir and ritonavir telaprevir telithromycin tipranavir and ritonavir troleandomycin voriconazole
Moderate CYP3A Inducers [a]	**Moderate CYP3A Inhibitors [b]**
bosentan efavirenz etravirine phenobarbital primidone	aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil

CYP: cytochrome P450.

[a] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (Accessed 27 May 2022).

[b] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (Accessed 27 May 2022).

Appendix F Examples of Clinical Inhibitors of Pgp

Drugs listed below that are inhibitors of Pgp are prohibited as concomitant medications with TAK-981.

Transporter	Gene	Inhibitor
Pgp	ABCB1	amiodarone carvedilol clarithromycin dronedarone itraconazole lapatinib lopinavir and ritonavir propafenone quinidine ranolazine ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir verapamil

Source: fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2 (Accessed 27 May 2022).

Pgp: P-glycoprotein.

Appendix G Contraception Methods

Male patients: We do not know if using TAK-981 will affect sperm or an unborn baby. Therefore, due to potential risk, you should not get your partner pregnant while taking TAK-981, and for 6 months after the last dose of study drug. Even if you are surgically sterilized (ie, have had a vasectomy), if you are sexually active with a woman who is pregnant or could get pregnant, you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) each time you have sex from the time of signing the informed consent form, and throughout the entire study drug treatment period, and for 6 months after the last dose of study drug. Or, you should completely avoid having heterosexual intercourse.

If your partner does become pregnant while you are taking part in the study, you must tell your study doctor immediately who will be able to advise you. In this situation, your partner should be under medical supervision during her pregnancy, and the baby should be under supervision after it is born. Your partner may be asked to give her consent to the collection of information related to both herself as well as the baby.

Female patients: We do not know if the study drug TAK-981 will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/infant, you must agree not to become pregnant or breastfeed a baby during the study and for 6 months after you stop taking TAK-981.

You must have a negative pregnancy test prior to enrolling in the study. This test will be repeated just before you start taking TAK-981 and then regularly throughout the study. If you become pregnant while on this study, the study drug will be stopped immediately, and the pregnancy will be followed until conclusion.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are postmenopausal), and if you are sexually active with a male partner who has not been sterilized, you must use 1 highly effective method of contraception and 1 additional effective barrier method of contraception at the same time from the time of signing the informed consent form, throughout the entire study drug treatment period, and for 6 months following the last dose of study drug. A postmenopausal state is defined as no menses (menstrual periods) for 12 months without an alternate medical cause.

Highly Effective Methods	Additional Effective Methods
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral. • Intravaginal. • Transdermal.	Male or female condom with or without spermicide (female and male condoms should not be used together).
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable. • Implantable.	Cap, diaphragm, or sponge with spermicide.
Intrauterine device (IUD).	Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
Intrauterine hormone-releasing system (IUS).	
Bilateral tubal occlusion.	
Vasectomised partner.	
Sexual abstinence.	

You must use birth control methods as directed above unless you completely avoid having heterosexual intercourse.

All patients (male or female): If you or your partner becomes pregnant while you are taking part in the study, you must tell your study doctor immediately who will be able to advise you regarding the possible risks to your unborn child and discuss options for managing the pregnancy. You will be asked for the results of any tests and procedures carried out during your pregnancy and up to the birth. You may also be asked for the results from any evaluation of the baby after the birth.

All patients considering having children in the future should consider autologous gamete cryopreservation (freezing their eggs or sperm) prior to enrolling in this study with TAK-981.

Appendix H BOIN Design

It is estimated that up to approximately 32 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981. Dose escalation will follow a BOIN design (Yuan et al. 2016). Approximately up to 4 patients will be enrolled in the first cohort. According to the BOIN design, the decision to escalate or de-escalate dose of TAK-981 is based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries. The target DLT rate for this study is 0.3. The dose escalation and de-escalation rules for TAK-981 are as follows.

1. If the observed DLT rate at the current dose level is ≤0.236, escalate.

2. If the observed DLT rate at the current dose level is ≥0.33, de-escalate.

3. Otherwise, stay at the same dose level.

The boundary guiding the number of patients treated at the current dose is displayed in the table below:

Number of Patients Treated at the Current Dose																				
Action	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Escalate if # of DLT ≤0.236	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4
De-escalate if # of DLT ≥0.33	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	7	7

The operating characteristics of the BOIN design based on 1000 simulations of each scenario are presented in the following table:

	1	**2**	**3**	**4**	**5**	**Number of Patients**	**% Early Stopping**
Scenario 1							
True DLT Rate	0.3	0.46	0.5	0.54	0.58		
Selection %	71.4	13.2	1.2	0.1	0		14.1
% pts. Treated	83.7	15.5	0.8	0.1	0	18.3	
Scenario 2							
True DLT Rate	0.16	0.3	0.47	0.54	0.6		
Selection %	29.2	57.8	10.8	0.7	0		1.5
% pts. Treated	54.6	36.9	8.2	0.3	0	19.8	
Scenario 3							
True DLT Rate	0.04	0.15	0.3	0.48	0.68		
Selection %	1.6	37.2	50.8	10	0.4		0
% pts. Treated	28.2	40.3	26.6	4.8	0.1	20	
Scenario 4							
True DLT Rate	0.02	0.07	0.12	0.3	0.45		
Selection %	0.1	5.5	39	46.2	9.2		0
% pts. Treated	22.7	27.8	30.2	17	2.3	20	

	1	2	3	4	5	Number of Patients	% Early Stopping
Scenario 5							
True DLT Rate	0.02	0.06	0.1	0.13	0.3		
Selection %	0.1	4	24.3	45.7	25.9		0
% pts. Treated	22.5	26.4	27.5	17.8	5.8	20	

DLT: dose-limiting toxicity.

The operating characteristics show that the proposed BOIN design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3. For example, in scenario 1, the first dose is the true MTD, and the BOIN design yields the high selection percentage of 71.4% with 16.7 patients allocated to this dose level.

Appendix I Protocol History

Date	Amendment Number	Region
22 June 2023	Amendment 6	Global
01 July 2022	Amendment 5	Global
09 September 2021	Amendment 4	Global
23 April 2021	Amendment 3	Global
10 February 2021	Amendment 2	Global
22 April 2020	Amendment 1	Global
19 February 2020	Original protocol	Global

Rationale for Amendment 5

This section describes the changes in reference to the protocol incorporating Amendment 5. The primary reason for this amendment was to expand Phase 2 enrollment in Cohort A to evaluate the dose regimen of TAK-981 at 120 mg once weekly (QW) in addition to the 90 mg twice weekly (BIW) dose regimen. This would add an additional 23 patients to the Phase 2 portion of the study. These data would be used to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

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

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 4.2.5 Nonclinical Toxicology	• Clarified that TAK-981–related effects after repeat daily or QW dosing, were observed in lung, endocrine systems and glandular organs in “rats only.” • Corrected dose of TAK-981 administered in rats.	Changes made to align with TAK-981 IB.
2	Section 4.2.6 Clinical Experience	Added details of Study TAK-981-1503 to the list of ongoing studies in TAK-981 program.	Addition made to reflect latest update in the program.
3	Section 4.4 Rationale for the Proposed Study	Updated details on DLTs observed in patients receiving TAK-981.	Update made to reflect information available in Recommended Phase 2 Dose Report for Study TAK-981-1002 (data cut off 30 April 2021).
4	Section 4.5.2 Rationale for the Phase 2 Dose of TAK-981 in TAK-981-1502	Added subsection on rationale for selection of Phase 2 dose of TAK-981 in this study.	Addition done to provide latest information available.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5	Section 4.5.3.2 Blood Section 9.4.17 DNA Measurements Appendix A SOE Table 3.b Biomarker Sample Collection During Phase 2	Added plasma sample collection for cell-free DNA evaluation.	Addition of samples to assess tumor mutation burden.
6	Section 2.0 STUDY SUMMARY Figure 6.a TAK-981-1502 Study Design Section 6.3 Phase 2–Expansion in Select Indications Section 6.4 Number of Patients Section 13.3 Determination of Sample Size	Expansion of Phase 2 enrollment in Cohort A to evaluate the dose regimen of TAK-981 120 mg QW in addition to the 90 mg BIW dose regimen and addition of 23 more patients to Phase 2.	Addition done to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.
7	Section 7.1 Inclusion Criteria	• For inclusion criterion #3 A, E, and G, patients must have not received more than 1 prior systemic therapy and must not have presented with disease progression during the first 6 months of treatment with first-line checkpoint inhibitor/anti-programmed cell death protein 1/protein 1 ligand–containing therapy, not 5 months. • For inclusion criterion #8 E, correction made to clarify the AST/ALT limits in patients with liver metastases.	Typographical error correction in criterion #3 E and G: 6 months is now listed, corrected from 5 months. The rationale is to align with the criteria for secondary resistance from the Society for Immunotherapy of Cancer Immunotherapy Resistance Taskforce. Typographical error correction in criterion #8 E to align summary and text.
8	Section 8.2 Definitions of DLT	Clarified that DLT definitions are applicable in Phase 1b.	Change made for more clarity.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9	Table 8.a General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs	Modified dose modification recommendations for TAK-981 in case of Grade 3 and Grade 4 non–life-threatening AEs (nonhematologic drug-related AEs). Added below exceptions that would not require TAK-981 dose reduction: • Grade ≥3 nausea, vomiting, and/or diarrhea resolved to Grade ≤1 or baseline within 72 hours with optimal antiemetics and/or antidiarrheal following local practice. • Transient Grade 3 fatigue (lasting <72 hours) and asymptomatic Grade ≤4 laboratory abnormalities that the investigator considers not clinically significant following agreement between sponsor and investigators.	Exceptions included to prevent dose modifications in case of transient and manageable non–life-threatening AEs, such as nausea and fatigue.
10	Section 8.5.4.3 COVID-19 Infection	Added subsection on coronavirus disease 2019 (COVID-19) infection.	Addition made to provide information on action to be taken if patient on study/study treatment is diagnosed with COVID-19 infection.
11	Section 8.7 Permitted Concomitant Medications and Procedures	Changed the time of recording concomitant medications in the electronic case report form (eCRF) from the time of first study drug administration to the time of patient's informed consent through the 30 (+10) days follow-up visit after the last dose of study drug.	Change made to align with eCRF guidelines and Appendix A SOE Table 1.a.
12	Appendix A SOE Table 1.a Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 1)	Updated footnote b.	Modification done for clarification of survival follow-up in Phase 1 patients.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13	Appendix A SOE Table 1.b Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 2)	Correction made in footnote l. Removed column for Day 15 in all Cycles, deleted footnote h and reordered subsequent footnotes.	Correction made to reflect correct days of performing hematology and chemistry assessments. Change made as Day 15 is not applicable in Phase 2.
14	Appendix A SOE Table 3.b Biomarker Sample Collection During Phase 2	Addition of new column for Predose Cycles 3, 6 and 9. Modified footnote a to provide information on which patients will have biomarker samples collected.	

Rationale for Amendment 4

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reason for this amendment was to update the translational strategy for sample collection for analysis of biomarkers in Phase 2.

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

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 4.2.2 Mechanism of Action	Corrected cross reference citations.	Correction.
2	Section 4.2.5 Nonclinical Toxicology Section 4.2.6 Clinical Experience Section 4.5.1 Rationale for the TAK-981 Starting Dose and Schedule Section 4.6.3 Potential Effects of TAK-981 Based on TAK-981 Clinical Studies	Updated clinical sections to include information from the latest investigator's brochure (IB) edition (Edition 4, data cutoff 28 June 2021).	Updated clinical data from the IB were available.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
3	Section 4.5.2 Rationale for the Tumor and Blood Tissues Collection Section 9.4.14.4 Fresh Paired Tumor Biopsy	Defined tumor collection as mandatory.	Clarified trial instructions for sites.
4	Section 5.1.3 Exploratory Objectives	Revised the following exploratory objective to: "To explore potential predictive biomarkers of response to combination therapy by exploring correlations between baseline molecular and cellular characterization of peripheral blood and tumor biomarkers (this may include genomic/transcriptomic/proteomic approaches) with efficacy and other clinical endpoints of interest."	Updated for clarity.
5	Section 8.1.1 TAK-981	Antipyretic medication treatment added for TAK-981 post-dose fevers.	Updated safety precautions.
6	Section 8.5.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle	Corrected cross references to sections describing treatment-emergent adverse events leading to permanent discontinuation of TAK-981 and criteria for reinitiation of pembrolizumab treatment.	Correction.
7	Table 8.a General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs	Added discontinuation of treatment in cases of Grade 3+ QTcF prolongation.	Updated safety precautions.
8	Table 8.d Pembrolizumab Dose Modification Guidelines for irAEs	Grade 3 nephritis and myocarditis reclassified with instructions to withhold drug. Addition of exfoliative dermatologic conditions.	Modification made as per pembrolizumab prescription sheet.
9	8.5.4.1 TAK-981 Criteria for Discontinuation	Criteria for Discontinuation for pembrolizumab were removed from criteria for discontinuation for TAK-981.	Clarification of the TAK-981 discontinuation criteria.
10	Table 9.e Primary Specimen Collection	Aligned order of specimens with the order of assessments in Appendix A, Table 3.a and clarified which specimens are mandatory during Phase 1 only.	Updated list of biomarker specimens for consistency.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
11	Section 9.4.16 Pharmacodynamic Measurements	Deletion of plasma cfDNA analysis.	Biomarkers sampling was streamlined.
12	Section 13.1.6 PK/Pharmacodynamic Analysis	Clarified which pharmacodynamic biomarkers are to be analyzed.	Clarification.
13	Appendix A Schedule of Events Table 1.a Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 1) Table 1.b Schedule of Events for Treatment Cycles (21-Day Cycle) (Phase 2) Table 2.a Plasma PK Sampling Schedule During Dose Escalation Table 2.b Plasma PK Sampling Schedule During Phase 2 Table 3.a Biomarker Sample Collection During Phase 1b Table 3.b Biomarker Sample Collection During Phase 2	Updated Appendix A schedule of event (SOE) table numbers as Tables 1.a, 2.a, 2.b, 3.a, and 3.b instead of Tables A-1, A-1.a, A-1.b, A-2, and A-3; added Table 1.b. Updated Table 1.a to add cross references to Tables 1.a through 3.b instead of showing sample collection times within the table; removed associated footnotes referring to the separate pharmacokinetic (PK) and pharmacodynamic SOEs. Updated Table 1.b and added Table 3.b to reflect streamlined PK and pharmacodynamic sample collection strategies, respectively, for Phase 2. Clarified that Table 3.a is for Phase 1b only and removed any Phase 2-specific sample collections and language.	Updates of SOE tables for consistency, Takeda style, and clarification. Update of PK SOE for Phase 2 and addition of pharmacodynamic SOE for Phase 2, reflecting streamlined sample collection strategy.
14	Appendix F Examples of Clinical Inhibitors of Pgp	Corrected source.	Correction.

Rationale for Amendment 3

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment were to incorporate additional local laboratory assessments for safety during Cycle 1, to update contraception requirements throughout the protocol, including in inclusion and exclusion criteria that specify contraception timelines, and to provide guidance on coronavirus disease 2019 (COVID-19) vaccination and procedures during the study.

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

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0 STUDY SUMMARY Study Design Section 6.3 Phase 2–Expansion in Select Indications	In the Phase 2 section, the paragraph describing the 2-stage design was reorganized for clarity and the sentence including "Cohorts E through G" was corrected to include "Cohorts E through H."	Edits for clarity and correction.
2	Section 2.0 STUDY SUMMARY Secondary Objectives Main Criteria for Evaluation and Analyses Section 5.1.2 Secondary Objectives Section 5.2.2 Secondary Endpoints	Moved assessment of TAK-981-small ubiquitin-like modifier (SUMO) adduct formation and SUMO pathway inhibition in blood to Phase 1b objectives and endpoints. Deleted pharmacokinetic endpoint from Phase 2; this endpoint is listed for both phases.	Update to limit target engagement assessments to Phase 1 dose escalation only. Edit to reduce redundancy.
3	Section 2.0 STUDY SUMMARY Main Criteria for Inclusion Section 4.6.2.5 Reproductive and Development Toxicity Section 7.1 Inclusion Criteria Section 8.8 Precautions and Restrictions Appendix G Contraception Methods	Updated text throughout the protocol to require patients to practice effective contraception through 6 months after the last dose of study drug (instead of 120 days after the last dose of study drug).	Compliance with local guidelines.
4	Section 2.0 STUDY SUMMARY Main Criteria for Evaluation and Analyses Sections 5.2.2 Secondary Endpoints Section 9.4 Study Procedures Section 9.9 Posttreatment Follow-up Assessments (Survival) Section 13.1.3.1 Primary Efficacy Analysis Section 13.1.3.2 Secondary Efficacy Analysis	Removed overall survival (OS) from list of secondary endpoints in Phase 1b. Added text to clarify that follow-up visits for progression-free survival (PFS) are to be conducted for any patients who discontinued for reasons other than progressive disease and follow-up for OS is to be done in Phase 2 only.	Modification to limit the OS analysis to patients on the pharmacodynamically optimal dose in Phase 2.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5	Section 2.0 STUDY SUMMARY Main Criteria for Evaluation and Analyses Section 5.2.1 Primary Endpoints Section 5.2.2 Secondary Endpoints Section 8.2 Definitions of DLT Table 8.c TAK-981 Dose Modification Guidelines for CRS 8.9.7 CRS Table 8.e CRS Management Recommendations Section 10.1.3 SAE Definition Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Changed criteria for grading cytokine release syndrome (CRS) from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS. Added guidelines for dose modification and CRS management based on ASTCT, including addition of corresponding references.	Alignment with other TAK-981 studies.
6	Section 4.6.6 Coronavirus Disease 2019 Pandemic	Added a section on benefit/risk assessment of participation in the study during the coronavirus disease 2019 (COVID-19) pandemic, indicating that the benefit/risk assessment remains favorable and that considerations for patient participation should be evaluated by the investigator on a patient by patient basis taking into consideration the current local situation, guidelines, and other recommendations.	Guidance on benefit/risk assessment for patient participation in the study during the COVID-19 pandemic.
7	Section 8.1.1 TAK-981	Updated text to indicate that if infusion reactions are observed, the length of the infusion can be extended up to 2 hours (instead of up to 4 hours) for all patients without requiring a protocol amendment.	Compliance with the TAK-981 stability at room temperature.
8	Section 8.1.3 Additional Instructions for Treatment Administration	Added that a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor.	Guidance on COVID-19 vaccination timing and procedures during the study.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9	Section 8.6 Excluded Concomitant Medications and Procedures	Added that vaccination during Cycle 1 is not permitted for patients in Phase 1.	Vaccination during Cycle 1 in Phase 1 would confound safety evaluation and determination of dose-limiting toxicities.
10	Section 8.7 Permitted Concomitant Medications and Procedures	Added guidance on timing of COVID-19 vaccination during the study including live attenuated vaccine must be completed at least 4 weeks prior to treatment initiation, vaccination not permitted during Cycle 1 in Phase 1, vaccination to be avoided within ±3 days of TAK-981 administration, and allowing a 7-day dose delay to accommodate vaccination.	Guidance on COVID-19 vaccination timing and procedures during the study.
11	Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Updated reporting period for pregnancies to 6 months after the last dose of study drug (instead of 12 months after the last dose of study drug.)	Alignment with updated contraception requirements per local guidelines.
12	Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Updated contact information for reporting medication errors.	Administrative update.
13	Section 13.1.3.2 Secondary Efficacy Analysis	Updated the definition of overall survival to be “the time from the date of the first dose administration to the date of death” instead of “the time from the date of randomization to the date of death”.	Correction.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14	Appendix A Schedule of Events Table 1 Schedule of Events for Treatment Cycles (21-Day Cycle)	Renamed the column header "PFS Follow-up" as "Survival Follow-up" and added the following footnote b to this header: "The survival status of patients in Phase 2 who permanently discontinue all study treatment for reasons specified in Section 9.7, with the exception of death, or withdrawal by the patient, will be assessed through medical charts or by telephone following the last administration of the study drugs." Added hematology and chemistry assessments on Days 4, 8, 11, and 15 of Cycle 1 with footnote m (previously footnote j) updated with the following text: "Day 4, 8, 11, 15 hematology and chemistry assessments are to be performed on dosing days depending on treatment schedule (these assessment may be discontinued during Phase 2)." Added that if a treatment visit is delayed, associated tests and procedures should also be delayed. Updated footnote k (previously footnote h) to include allowances for dose delays, including a dose delay of up to 7 days to accommodate for COVID-19 vaccination. Updated footnote r (previously footnote o) to clarify that imaging frequency after 6 months should be reduced to every 3 months until occurrence of progression of disease. Rearranged order of pharmacodynamic biomarker sample collections to match that in the pharmacodynamic biomarker table in Appendix A (Table 2) and aligned sample collection times with those in Table 2.	Allowance of additional monitoring measures for platelets and red blood cells during treatment. Guidance on COVID-19 vaccination timing and procedures during the study. Clarification of follow-up procedures.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
15	Appendix A Schedule of Events Table 2 Biomarker Sample Collection	Added columns for Cycle 3 and beyond to show sample collection predose on Days 1 and 8. Added samples at Cycle 2 Day 8 for chemokines/cytokines and RNA (pre-dose and 6-8 hours post-end of infusion [EOI]) and removed peripheral blood mononuclear cells sample for immunophenotyping from 6-8 hours post-EOI.	Updates to biomarker collection schedule at Cycle 2 Day 8 and addition of columns for sample collection at Cycles 3 and beyond.
16	Appendix E Drugs That Interact With the CYP3A Family of CYPs	Under strong cytochrome P450 (CYP) 3A inhibitors, corrected spelling of nefazodone and telithromycin and deleted grapefruit. Updated source table number in footnote a and added footnote b to separate sources for CYP3A inducers and inhibitors.	Update to align with current Food and Drug Administration guidance.

Rationale for Amendment 2

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reason for this amendment was to incorporate additional tumor histologies in Phase 2.

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

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	Clarified that the follow-up period includes monitoring of both disease and survival status.	Clarification.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2	Section 2.0 STUDY SUMMARY Section 4.5 Rationale for the Proposed Patient Population Figure 6.a TAK-981-1502 Study Design Section 6.3 Phase 2–Expansion in Select Indications	Updated the list of cohorts to be evaluated in Phase 2 to the following 8 cohorts: Cohort A: non-squamous non-small cell lung cancer (NSCLC); Cohort B: cervical cancer; Cohort C: microsatellite stable colorectal cancer (MSS-CRC); Cohort D: cutaneous melanoma; Cohort E: squamous NSCLC; Cohort F: small cell lung cancer (SCLC); Cohort G: head and neck squamous cell carcinoma (HNSCC); and Cohort H: microsatellite instability high/ mismatch repair deficient colorectal cancer (MSI-H/dMMR CRC). Conditioned opening of Cohorts E, F, G, and H to a positive Stage 1 readout for Cohorts A, B, C, or D.	Further evaluation of the activity of TAK-981 in combination with pembrolizumab at the recommended Phase 2 dose (RP2D) in additional tumor types.
3	Section 2.0 STUDY SUMMARY Section 6.3 Phase 2–Expansion in Select Indications	Added text that enrollment may be paused at the end of Stage 1 of each arm and deleted text on possible enrollment into Stage 2 in case of potential clinical benefit.	Clarification on process of initiating enrollment in Stage 2.
4	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Added durable response rate (DRR) and time to response (TTR) as part of the secondary efficacy objective for Phase 2.	Update of efficacy endpoints for Phase 2.
5	Section 2.0 STUDY SUMMARY Section 6.4 Number of Patients Section 13.3 Determination of Sample Size	Increased the estimated number of enrolled patients from 101 to 242 and increased the number of sites from 30 to 60 to account for additional cohorts in Phase 2.	Incorporation of additional cohorts during Phase 2.
6	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Edited inclusion criterion 3 to update entry criteria for NSCLC and to add entry criteria for squamous NSCLC, SCLC, HNSCC, cutaneous melanoma, and MSI-H/dMMR CRC.	Updates for further evaluation of the activity of TAK-981 in combination with pembrolizumab at the RP2D in additional tumor types.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Added the following as inclusion criterion 5: Patients in Phase 2 expansion cohorts must have a programmed cell death protein 1 ligand (PD-L1) result in tumor tissue obtained from a Food and Drug Administration (FDA)-approved PD-L1 test.	Characterization of the molecular and histological profile of the tumor tissues of patients enrolled in Phase 2.
8	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Renumbered inclusion criterion 6 to inclusion criterion 7 and updated it to include a screening creatinine clearance requirement of ≥30 mL/min (instead of ≥45 mL/min) per Cockcroft-Gault formula.	The creatinine clearance requirement was lowered based on recent pharmacokinetic (PK) analysis that showed minimal renal elimination of TAK-981.
9	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	In exclusion criterion 10, added that the washout period for P-glycoprotein inhibitors is 1 week before TAK-981 dosing.	Clarification.
10	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Deleted examples of live vaccine from exclusion criterion 11.	Clarification.
11	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints	Added DRR and TTR as secondary endpoints.	Update of secondary efficacy endpoints.
12	Section 2.0 STUDY SUMMARY Section 4.5.1 Rationale for the TAK-981 Starting Dose and Schedule Section 8.1 Study Drug Administration Section 8.4 Phase 1b Dose Escalation Rules Section 13.3 Determination of Sample Size	Updated the dosing schedules to be evaluated to include a schedule of Days 1 and 8 in 21-day cycles in addition to the schedule of Days 1, 4, 8, and 11 in 21-day cycles. Two alternative TAK-981 dosing schedules were also added: Day 1 or Days 1, 8, and 15 in 21-day cycles.	Update to allow additional dosing schedules within the dose escalation phase in order to evaluate safety and pharmacodynamics/PK characteristics of TAK-981.
13	Section 4.1.3 Colorectal Cancer Section 4.1.4 Small Cell Lung Cancer Section 4.1.5 Head and Neck Squamous Cell Carcinoma Section 4.1.6 Cutaneous Melanoma	Added background information for added indications.	Update information on the added tumor types.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14	Section 4.2.6 Clinical Experience	Updated clinical section to include text from the latest investigator's brochure (Edition 3, data cutoff 28 June 2020).	Updated clinical data from the investigator's brochure were available.
15	Section 4.5.2.2 Blood	Updated the description of the types of blood biomarkers to be evaluated to include cellular markers of natural killer and T cell activation.	Clarification.
16	Section 5.1.3 Exploratory Objectives	Updated exploratory objectives to indicate that potential predictive biomarkers are to be explored and that certain exploratory endpoints were to be evaluated to further understand the TAK-981 mechanism of action and potential responsive patient populations.	Clarification.
17	Section 6.3.1 Early Stopping Rules	Added early stopping rules for enrollment of cohorts in Phase 2.	Alignment with TAK-981 study protocols.
18	Section 6.6.1 Duration of an Individual Patient's Study Participation	Clarified that patients will be followed for survival (rather than progression-free survival [PFS]) for up to 12 months after the last dose of study drug.	Alignment with the overall survival (OS) objective in Phase 2.
19	Table 6.a Primary and Secondary Endpoints for Disclosures	Added disease control rate (DCR), DRR, time to progression (TTP), and OS as secondary endpoints for disclosure for Phase 2.	Alignment with secondary objectives in Phase 2.
20	Section 8.1.1 TAK-981	Updated the storage temperature for TAK-981.	Alignment with the requirements in the TAK-981 Pharmacy Manual.
21	Table 8.d Pembrolizumab Dose Modification Guidelines for irAEs	Corrected the monitoring of hypothyroidism to include monitoring of thyroid function instead of renal function.	Correction.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
22	Section 9.4.3 Medical History	Clarified which disease-related medical history data were to be collected, including tumor pathology/cytogenetic/mutational information, human papillomavirus status, and tumor mutational burden, and PD-L1 results. Clarified that PD-L1 tumor status was required from all patients in Phase 2.	Clarification.
23	Table 9.c Tumor Prognostic Markers	Added a table of prognostic markers for colon cancer and cervical cancer.	To better evaluate complete responses per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.
24	Table 9.e Primary Specimen Collection	The list of specimens to be collected was updated to change the sample name from "blood sample for immunophenotyping" to "peripheral blood mononuclear cell (PBMC) sample for immunophenotyping" and to add a sample called "blood cells for immunophenotyping."	Clarification on specimen collection.
25	Section 9.4.16 Pharmacodynamic Measurements	Updated the list of pharmacodynamic measures to include immunophenotyping in PBMCs and analyses of pharmacodynamic measures in the interferon pathway.	Clarification.
26	Section 10.1.4 AESI Definition Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Clarified reporting procedures for adverse events (AEs) of special interest.	Clarification.
27	Section 10.3 Monitoring of AEs and Period of Observation	Aligned reporting period for AEs with schedule of events.	Clarification.
28	Section 13.1.1 Analysis Sets Section 13.1.3.1 Primary Efficacy Analysis	Renamed an analysis set from "Phase 2 primary analysis set" to "Phase 2 efficacy analysis set" and clarified definition.	Clarification.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
29	Section 13.1.3.1 Primary Efficacy Analysis	For the Phase 2 analysis, defined overall response rate (ORR) as based on RECIST, Version 1.1 instead of iRECIST (consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials).	Alignment with the primary objective.
30	Section 13.1.3.1 Primary Efficacy Analysis	Added DRR and TTR to the list of efficacy parameters that may be summarized in Phase 1b. For estimates of ORR, added that additional confidence intervals may also be provided as appropriate.	Clarification and addition of DRR and TTR.
31	Section 13.1.3.2 Secondary Efficacy Analysis	Added DRR and TTR to the list of secondary endpoints and reordered the list to align with other protocol sections. Added definitions for DRR, TTR, TTP, and OS. Added that estimates of ORR, DCR, and DRR will be presented with 2-sided 95% exact binomial confidence intervals, with additional confidence intervals provided as appropriate, that PFS, OS, duration of response, and TTP will be analyzed using Kaplan-Meier method for the Phase 2 efficacy analysis set and TTR summarized for responders, and that all efficacy endpoints may be analyzed for the overall study population as appropriate.	Clarification and addition of DRR and TTR.
32	Section 13.3 Determination of Sample Size	The alpha level for sample size calculations for all cohorts was changed from 2-sided to 1-sided.	Correction of text to align with other TAK-981 protocols.
33	Section 13.3 Determination of Sample Size	Added sample size calculations for the additional Cohorts D and H.	Incorporation of additional cohorts in Phase 2.
34	Section 14.1 Study-Site Monitoring Visits	Text was added to allow for potential remote monitoring of sites due to the COVID-19 (coronavirus disease 2019) pandemic.	Clarification.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
35	Appendix A Schedule of Events	The schedules of events for Cycle 1 was updated to add alternative dosing schedules with associated changes in assessments, to add an Eastern Cooperative Oncology Group (ECOG) assessment 90 days after the last dose visit, to add flexibility for timing of vital sign measurements before and after dosing of each study drug, and to clarify timing of pregnancy testing and cell-free DNA (cfDNA) sample collection.	Modifications to simplify vital signs assessment and procedures across the TAK-981 clinical studies.
36	Appendix A Schedule of Events	The schedule of events for Cycle 2 and Cycles 3 and subsequent cycles was updated to remove collection of the hematology/chemistry sample on Day 8 of Cycle 3 and subsequent cycles, to add collection of immunosafety markers at end of treatment, to add collections of PBMCs samples for immunophenotyping and blood samples for cfDNA, and to add flexibility for timing of vital sign measurements before and after dosing of each study drug.	Modifications to simplify vital signs assessment and central and local laboratory assessments across the TAK-981 clinical studies.
37	Appendix E Drugs That Interact With the CYP3A Family of CYPs	The list of CYP3A inhibitors and inducers was updated based on the most recent recommendations from FDA (3 March 2020).	Alignment with recent FDA recommendations.
38	Appendix H BOIN Design	Renumbered tables and deleted 2 references included in the appendix.	Editorial changes.

Rationale for Amendment 1

This section describes the changes in reference to the protocol incorporating Amendment 01. The primary reason for this amendment was to incorporate requirements by the United States Food and Drug Administration (FDA).

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

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Clarified that starting dose for TAK-981 will be 40 mg.	Clarification provided in response to FDA request.	Section 4.5.1 Rationale for the TAK-981 Starting Dose and Schedule Section 8.4 Phase 1b Dose Escalation Rules Section 2.0 STUDY SUMMARY
2. Modified inclusion criteria to require NSCLC patients with driver mutations/genomic aberrations must have progressed after therapy with FDA-approved targeted therapy.	Change made in response to FDA request.	Section 7.1 Inclusion Criteria, criterion #3A Section 2.0 STUDY SUMMARY
3. Modified inclusion criteria to clarify that CPI-naïve MSS-CRC patients must have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens if indicated.	Change made in response to FDA request.	Section 7.1 Inclusion Criteria, criterion #3C Section 2.0 STUDY SUMMARY
4. Removed inclusion criterion #5 and note in the inclusion criterion #4 that required mandatory tumor biopsy from patients in Phase 2, Stage I.	Change made in response to FDA request.	Section 4.5.2.1 Tumor Biopsies Section 7.1 Inclusion Criteria Section 9.4.14.2 Tumor Biopsies Section 9.4.14.4 Fresh Paired Tumor Biopsy Section 9.4.16 Pharmacodynamic Measurements Table 9.d Primary Specimen Collection Appendix A: Table 1, footnote “q”; Table 2, footnote “b” Section 2.0 STUDY SUMMARY
5. Added criteria to exclude patients with baseline prolongation of the QT interval	Change made in response to FDA request.	Section 7.2 Exclusion Criteria, criterion #8. Section 2.0 STUDY SUMMARY
6. Added study-stopping rules during dose escalation.	Change made in response to FDA request.	Section 6.2 Phase 1b–Dose Escalation
7. Modified definitions of DLT.	Change made in response to FDA request.	Section 8.2 Definitions of DLT

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
8. Added language for precautionary measures to be taken during dose escalation phase by staggering the enrollment.	Change made in response to FDA request.	Section 4.6.2.3 IRRs and Potential for CRS Section 6.2 Phase 1b–Dose Escalation Section 2.0 STUDY SUMMARY
9. Added a 90-day follow up visit after last dose with the study treatment to capture any late-onset immune-related adverse events (irAE).	Change made in response to FDA request.	Section 6.1 Overview of Study Design. Section 9.4 Study Procedures Section 9.7.1 Treatment Beyond Progression Section 10.3 Monitoring of AEs and Period of Observation Section 2.0 STUDY SUMMARY Appendix A, Table 1
10. Amended language to remove treatment beyond 24 months.	Change made in response to FDA request.	Section 6.6.1 Duration of an Individual Patient's Study Participation Section 6.6.2 End of Study/Study Completion Definition and Planned Reporting Section 6.6.5 Posttrial Access Section 2.0 STUDY SUMMARY
11. Amended language for intrapatient dose escalation.	Change made in response to FDA request.	Section 8.5.1 Intrapatient Dose Escalation
12. Added adverse event of special interest (AESI) definition, procedure for recording and reporting AESIs, and monitoring of AESIs.	Change made in response to FDA request.	Section 10.0 ADVERSE EVENTS Section 13.1.7 Safety Analysis Appendix A, Table 1
13. Added text to perform hematology and coagulation tests prior to biopsy procedure to assess the risk of bleeding associated with biopsy procedure.	Change made in response to FDA request.	Section 9.4.14.4 Fresh Paired Tumor Biopsy Appendix A, Table 1 and Table 2

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
14. Specified the names of countries and regions in which this study might be conducted.	Clarification provided in response to FDA request.	Section 2.0 STUDY SUMMARY
15. Added details on TAK-981 preparation.	Addition made in response to FDA request.	Section 8.1.1 TAK-981
16. Amended and added text in rationale for the proposed study.	Change made to provide current data.	Section 4.4 Rationale for the Proposed Study
17. Added exploratory endpoint of TAK-981-SUMO adduct formation and SUMO pathway inhibition in tumor tissue.	Change made in response to FDA request regarding fresh paired tumor biopsies.	Section 5.2.3 Exploratory Endpoints
18. Modified figure for study design.	Change made to reflect study design.	Figure 6.a TAK-981-1502 Study Design
19. Amended number of patients to be enrolled in the study.	Change made in response to FDA request.	Section 6.4 Number of Patients Section 13.3 Determination of Sample Size Section 2.0 STUDY SUMMARY
20. Amended upper bound for the targeted toxicity interval for maximum tolerated dose (MTD) not to exceed 33% and provided the operating characteristics of the Bayesian optimal interval design (BOIN) that will be used for dose-escalation in the phase 1b part of study.	Change made in response to FDA request.	Section 8.4 Phase 1b Dose Escalation Rules Appendix H BOIN design
21. Added definition of Phase 2 primary analysis set.	Addition made in response to FDA request.	Section 13.1.1 Analysis Sets
22. Amended that ECOG will be conducted within 3 days before dosing on Day 1 of each treatment cycle.	Clarification provided per Investigator's recommendation.	Appendix A, Table 1
23. Added language to address study conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.	Change made to facilitate conduct of study activities during COVID-19 pandemic.	Appendix A, Table 1 footnotes

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
24. Removed the requirement of patient to stay in supine position for ECGs and blood pressure measurements.	Change made per Investigator's request.	Section 9.4.11 Cardiac Monitoring Appendix A, Table 1 footnotes "e" and "h"
25. Clarified that blood sample for DNA will be collected on Cycle 1 Day 1 predose	Change made per Investigator's request.	Section 9.4.17 DNA Measurements Appendix A, Table 1 and Table 2
26. Added window periods for biomarker samples collection at 1h, 4h and 24 h in Cycle 1 Day 1 and Cycle 1 Day 8 and at 1h and 4h in Cycle 2 Day 8.	Change made to facilitate sample collection at the clinical site.	Appendix A, Table 2
27. Added blood sample collection for cfDNA.	Addition made to assess potential biomarkers for monitoring disease status	Appendix A, Table 1 (and footnote "u") and Table 2 (and footnote "d")

Signature Page for TAK-981-1502 Protocol Amend 6 2023-06-22
Title: A Phase 1b/2 Study of TAK-981 Plus Pembrolizumab to Evaluate the Safety, Tolerability, and Antitumor Activity of the Combination in Patients With Select Advanced or Metastatic Solid Tumors

Approval	PPD Clinical 27-Jun-2023 20:02:18 GMT+0000

Approval	PPD Statistics 27-Jun-2023 20:12:17 GMT+0000

Approval	PPD Clinical 27-Jun-2023 20:13:50 GMT+0000

Document Number: TDN-000182163 v1.0