Statistical Analysis Plan

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 2, 8 Nov 2024

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-981-1502

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

PHASE 1b/2

Version: **Amendment 2.0**

Date: 8 November 2024

Prepared by:

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1.1 Approval Signatures

Study 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

Approvals:

[redacted], PhD — Date

[redacted], Oncology Statistics

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AUC_{∞}	area under the plasma/blood/serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BOIN	Bayesian Optimal Interval Design
cfDNA	cell-free DNA
CPI	checkpoint inhibitor
CL	total clearance after intravenous administration
C_{max}	maximum observed concentration
C_{max} (t_{max}).	time of first occurrence of C_{max}
CR	complete response
CRC	colorectal cancer
CRS	cytokine release syndrome
DLT	dose-limiting toxicity
DOR	duration of response
DOSD	duration of stable disease
DRR	durable response rate
BOR	Best Overall Response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
IFN	interferon
irAE	immune-related adverse event
iRECIST	consensus guideline developed by the RECIST Working Group for the use of modified RECIST, Version 1.1 in cancer immunotherapy trials
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA
MSI-H	microsatellite instability, high levels
MSI-L	microsatellite instability, low levels
MSS	microsatellite stable
MSS-CRC	microsatellite stable colorectal cancer

Abbreviation	Term
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
PAD	pharmacologically active dose
PD	progressive disease (disease progression)
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
PK	pharmacokinetic(s)
PR	partial response
q21d	every 21 days
QTc	corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SMC	Safety Monitoring Committee
SUMO	small ubiquitin-like modifier
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	first time to reach maximum (peak) plasma concentration
TEAE	treatment-emergent adverse events
TTP	time to progression
TTR	time to response
WHO	World Health Organization
SAP	Statistical Analysis Plan
TLFs	Tables, Listings, and Figures
CSR	Clinical study report

4.0 OBJECTIVES

4.1 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.

4.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of TAK-981 in combination with pembrolizumab.

Phase 1b:

- 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.

4.3 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 (this may include genomic/transcriptomic/proteomics approaches) with efficacy and other clinical endpoints of interest.
- To explore mechanisms of resistance in peripheral blood and tumor samples collected from patients who initially respond to TAK-981 in combination with pembrolizumab therapy and then exhibit disease progression (PD).
- Exploratory endpoints, such as evaluating circulating serum proteins, cell-free DNA (cfDNA), exosomes, and miRNA 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.

4.4 Study Design

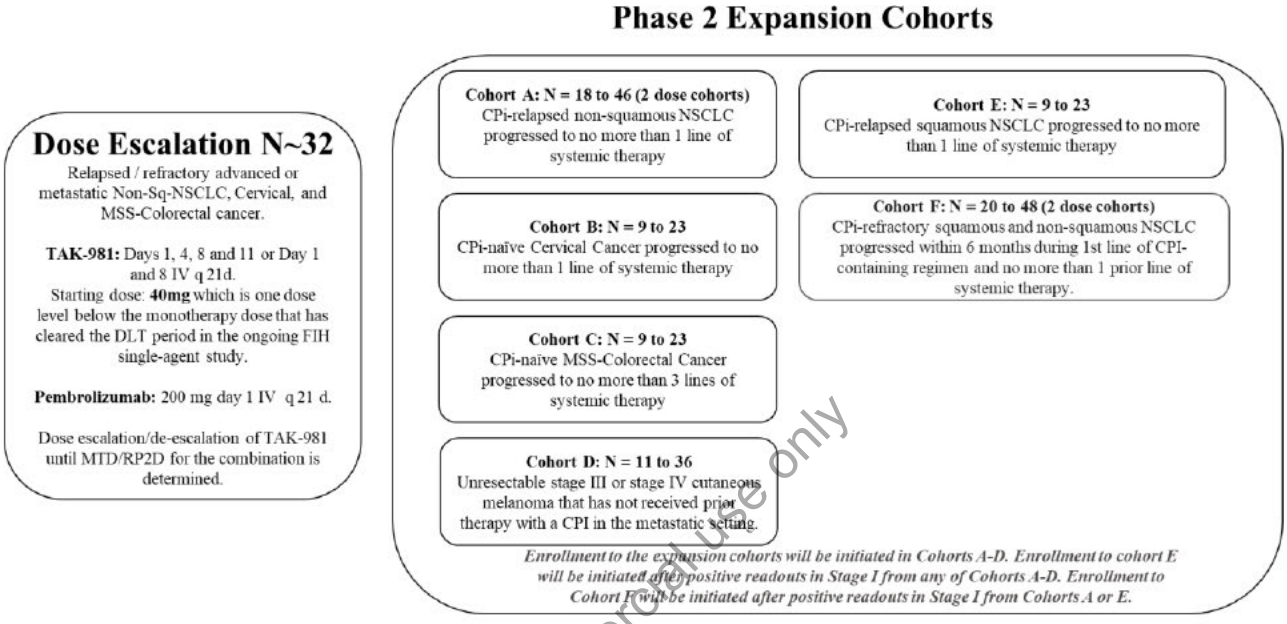
The study consists of 2 phases, phase 1b (Dose Escalation), and phase 2 (Expansion in Selected Indications).

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 30 and 90 days after the last dose occurring when treatment is discontinued for any reason, and a progression-free survival (PFS) follow-up period lasting for a maximum of 12 months for each patient after their last dose of study drug to monitor 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 PD, unacceptable toxicity, or any criterion for withdrawal from the study or study drugs occurs.

The overall study design is displayed in Figure 4.a.

Figure 4.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.

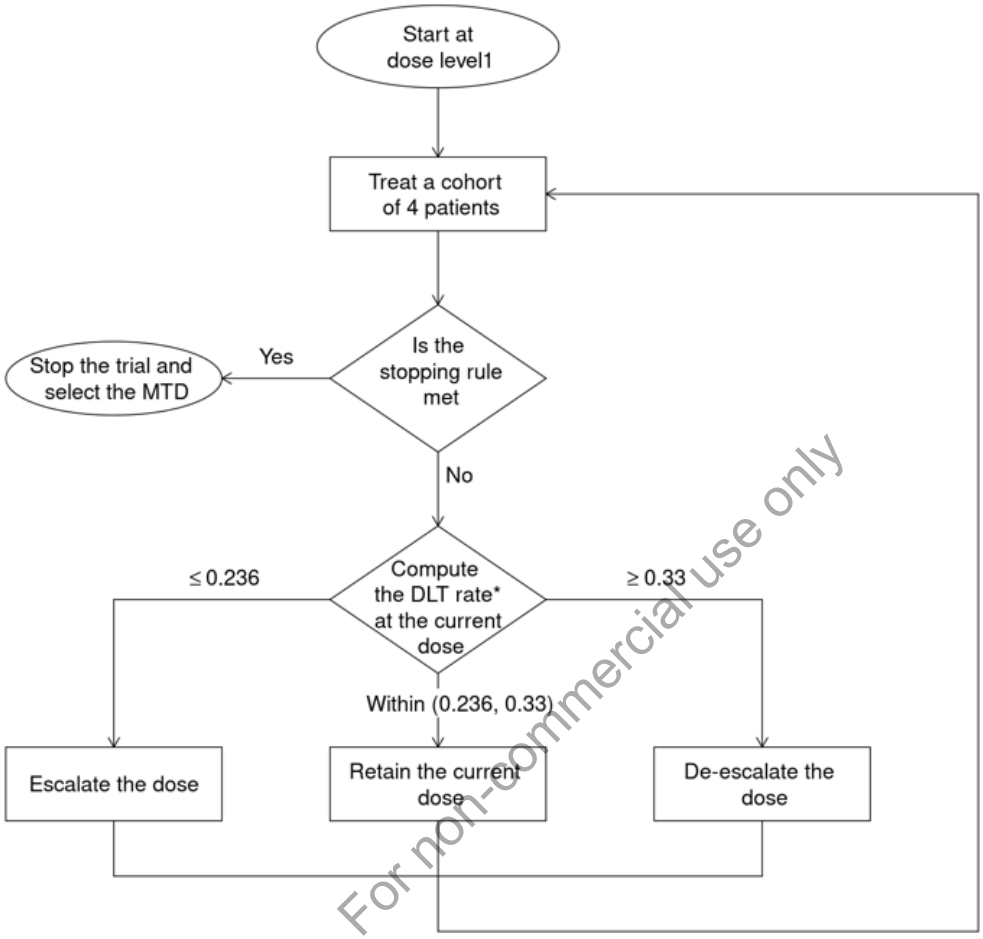
Phase 1b: Dose Escalation

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 non-small cell 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 (BOIN) design [1], to determine 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 events (irAEs) across all patients beyond the DLT window, preliminary pharmacokinetic (PK) data, preliminary pharmacodynamic data, preliminary translational data and any early antitumor activity observed along with the statistical inference from the BOIN.

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.

The schema of the dose escalation is presented in Figure 4.b.

Figure 4.b Phase 1b Dose Escalation Schema



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

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.

Each cohort 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 6.0) 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. The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have had the opportunity complete the 6-month disease assessment. Enrollment to the expansion cohorts 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).

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 in the protocol) 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.

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.

5.0 ANALYSIS ENDPOINTS

5.1 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 Secondary Endpoints

The secondary endpoints are:

- TAK-981 plasma concentration-time data.

Phase 1b:

- ORR, DCR, DRR, DOR, DOSD, 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.

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, DOSD, 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.

5.3 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 miRNA signatures associated with response or resistance to TAK-981 in combination with pembrolizumab treatment will be executed as warranted.

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that up to 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 RP2D in patients with select advanced or metastatic solid tumors, such as NSCLC, cervical, and CRC.

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).

Alternative TAK-981 dosing schedules (eg, Day 1, or Days 1, 8, and 15 in 21-day cycles) may be explored. Therefore, it is estimated that up to approximately 32 DLT-evaluable patients will be enrolled in this study for the dose escalation phase with a dose escalation of TAK-981 in combination with pembrolizumab at a fixed dose.

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 concurrently 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 [2] 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-G) 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-G) 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 6.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 , 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 one-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 6.b).

Table 6.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 (p0 ≤ 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 6.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	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
Response at the end of Stage 1				
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 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will display the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data.

All available efficacy and safety data will be included in data listings and tabulations as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

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

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

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

Screen failure subjects will be grouped and listed at the end.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it was collected unless otherwise specified. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

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

7.1.3 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then impute to first dose date
  - If month and year are different than month and year of first dose date, then impute to first date of the month
- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be used instead
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then it is imputed with 1st dose date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date.

Adverse events with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed

- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However, if it is to be done, the rules are outlined above. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

7.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
  - If year is known, but day and month are missing, then 1st of January of the year will be imputed
- If all is missing, then impute date to Date of Birth (DOB)
  - If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB)

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, then impute date to 31st of December in the year of last dose

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not

occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

7.1.5 Conventions for Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.
- When only a year is present,
  - If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.
- If no components of the onset date are present the date of last dose + 1 will be imputed.

7.2 Analysis Sets

The Analysis Sets (Analysis Populations) 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 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.

The DLT-evaluable set will be used to determine the RP2D/MTD.

Response-evaluable analysis set: Patients who met all inclusion criteria and none of the exclusion criteria, have received at least 1 dose of study drug, have sites of measurable disease at baseline, and 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 met all inclusion criteria and none of the exclusion criteria, and have 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*.

7.3 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each population, and will be presented by escalation cohort and overall for phase 1b, and by each expansion cohort and overall for phase 2. The primary reason for study termination will also be summarized similarly in this table.

All percentages will be based on the number of patients in the safety population.

A listing will present data concerning patient disposition.

7.4 Demographic and Other Baseline Characteristics

Demographics will be summarized by dose escalation cohort and overall for phase 1b, and by each expansion cohort and overall for phase 2. Demographic data will also be presented in a by-patient listing. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters if applicable. Age will be calculated from date of birth to date of informed consent.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

At study entry, disease characteristics for each indication, disease primary diagnosis, disease type, Eastern Cooperative Oncology Group (ECOG) performance status, disease staging, tumor identification, prior interventions, prior radiotherapy, and other parameters will be summarized if applicable.

In addition, for each cancer type, Histologic Type of Cancer, PD-L1 status, test used for PD-L1 status, PD-L1 score, TPS score, CPS score, Tumor Mutational Burden (TMB) assessment, Tumor diagnostic biomarkers, and detection types will be summarized. The detailed disease specific characteristics are as follows:

- Cohort A, E, F: Disease specific Biomarkers (including EGFR, ALK, ROS1, KRAS, MET, NTRK, FGFR, HER2, BRAF, PIK3CA, RET, DDR2, PTEN, Protein and Other).
- Cohort B: Disease specific Biomarkers (including EGFR, ALK, ROS1, KRAS, MET, NTRK, FGFR, HER2, BRAF, PIK3CA, RET, DDR2, PTEN and Other), HPV association status, E6/E7 Protein, E6/E7 RNA, E6/E7 RNA Method and p16 Protein Expression.
- Cohort C, H: Disease specific Biomarkers (including EGFR, ALK, ROS, MET, NTRK, FGFR, HER2, PIK3CA, RET, DDR2, PTEN and Other), KRAS Mutation, BRAF Mutation and Tumor Mutational Burden (TMB).
- Cohort D: Disease specific Biomarkers (including EGFR, ALK, ROS1, KRAS, MET, NTRK, FGFR, HER2, BRAF, PIK3CA, RET, DDR2, PTEN, Protein and Other).
- Cohort G: Disease specific Biomarkers (including EGFR, ALK, ROS1, KRAS, MET, NTRK, FGFR, HER2, BRAF, PIK3CA, RET, DDR2, PTEN, Protein and Other), HPV association status, E6/E7 Protein, E6/E7 RNA, E6/E7 RNA Method and p16 Protein Expression and Primary Tumor Site At Initial Diagnosis.

7.5 Medication History and Concomitant Medications

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (whether it is resolved or ongoing).

A separate table will summarize the numbers and percentages of patients who received prior therapy, including prior anticancer, prior radiation, prior surgery or procedure, prior radiotherapy and best response to the last prior anticancer therapy.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by ATC Pharmacological Subgroup and WHO drug generic term for the safety population, from the signing of ICF through 30 days after the last dose of study treatment, or to the start of subsequent systemic anticancer therapy, whichever occurs first.

Concomitant medications will also be presented in a by-patient listing.

Concomitant procedures will not be coded but will be presented in a by-patient listing.

7.6 Study Drug Exposure and Compliance

Extent of Exposure:

The exposure to each of the study drugs (TAK-981 and Pembrolizumab) will be characterized by total amount of dose taken in mg, total number of doses taken, relative dose intensity (%), number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, ≥3, ≥6, ≥9, ≥12 and ≥15 treated cycles for patients in the safety population. A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Duration of treatment (days), and number and percentages of patients who had >=3, >=6, … weeks of treatment will be summarized for patients in the safety population, where duration of treatment (days) is calculated as (last dose date of study drug – first dose date of study drug + 1).

Descriptive statistics for Relative dose intensity (RDI) (%) and categorical summary of RDI (<50%, 50% to <80%, 80% to < 100%, =100%, >100%) will be summarized will be presented overall and by cycle.

Overall RDI (%) is defined as 100 x (Total amount of dose taken) / (Total prescribed dose of all treated cycles), where a treated cycle is defined as a cycle in which the patient received any amount of any study drug.

For RDI by cycle the similar formula is used as overall relative dose intensity and will be calculated for treated cycles.

Cycle RDI (%) is defined as 100 x (Total amount of dose in cycle) / (Total prescribed dose in cycle). The extent of exposure will be summarized by escalation cohort, overall for dose escalation phase, by safety expansion cohort, and overall in safety expansion phase.

Dosing data will also be presented in a by-patient listing.

Action on Drug:

Action on study drug will be summarized by Cycles 1 - 6, Cycle 7 - 12, Cycles 13 - 18, Cycle ≥ 19 and total, for each dose escalation cohort, overall for dose escalation phase, for each dose expansion cohort and overall in dose expansion phase, and overall for both phases combined.

7.7 Efficacy Analysis

7.7.1 Primary Efficacy Endpoint(s)

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, PFS, and OS may be summarized as appropriate. Disease response will be categorized and presented in listings.

Phase 2:

The primary endpoint for the 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 response-evaluable analysis set. Estimates of the ORR (CR + PR) will be presented with 2-sided 95% exact binomial confidence intervals.

7.7.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include DCR, DRR, DOR, TTR, TTP, and PFS as assessed by the investigator according to both RECIST, Version 1.1 and iRECIST; ORR as assessed by the investigator according to iRECIST; and OS. Response related efficacy endpoints by RECIST Version 1.1 are defined and analyzed as below; the ones by iRECIST will be defined and analyzed similarly.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve SD or better (determined by the investigator) >6 weeks during the study in the response-evaluable population.

The DCR will be summarized by frequencies and percentages based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on the phase 2 response-evaluable analysis set by expansion cohort, and overall in expansion phase. Estimates of the DCR will be presented with 2-sided 95% exact binomial confidence intervals.

Durable Response Rate (DRR)

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.

The DRR will be summarized by frequencies and percentages based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on the phase 2 response-evaluable analysis set by expansion cohort, and overall in expansion phase. Estimates of the DRR will be presented with 2-sided 95% exact binomial confidence intervals.

Duration of Response (DOR)

The DOR will be calculated for responders with a PR or better in the tumor response-evaluable analysis set. DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better.

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

The Kaplan-Meier method will be used to estimate the distribution of DOR when data allows. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence

intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

Time to Response (TTR)

TTR is defined as the time from the date of first study drug administration to the date of first documentation of objective response (PR or better) by the investigator.

Patients with no PR or better will be censored on the last date of adequate response assessment. Patients with no post baseline response assessment will be censored on date of first dose.

TTR (months)= (date of response or censor – date of first dose + 1)/30.4375).

The analysis of TTR will be based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on the phase 2 response-evaluable analysis set by expansion cohort, and overall in expansion phase. The Kaplan-Meier method will be used to estimate the distribution of TTR (if data allows) by escalation cohort, overall for dose escalation phase, by expansion cohort, and overall in expansion phase. Kaplan-Meier curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley, and Kaplan-Meier estimates with 95% CIs at 3 and 6 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.

Time to Progression (TTP)

TTP is defined as the time from the date of the first dose to the date of the first documentation of PD as assessed by the investigator. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment. Patients who die during treatment without PD will also be censored at the date of last response assessment. Patients who received any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to or on the date of initiation of the subsequent anticancer therapy. Patients with no post baseline response assessment will be censored on date of first dose.

The analysis of TTP will be based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on response-evaluable analysis set by expansion cohort, and overall in expansion phase. The Kaplan-Meier method will be used to estimate the distribution of TTP. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

Progression Free Survival (PFS)

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 RECIST version 1.1 or iRECIST for patients. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better. Patients who received any subsequent anticancer therapy without a prior reported progression will be censored at the

last response assessment prior to or on the date of initiation of the subsequent anticancer therapy. Patients with no post baseline response assessment will be censored on date of first dose.

The analysis of PFS will be based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on response-evaluable analysis set by expansion cohort, and overall in expansion phase. The Kaplan-Meier method will be used to estimate the distribution of PFS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier PFS probability estimates with 95% CIs at 3, 6 and 12 months (or later time points if data permits) will be presented. The number of patients with events along with the type of events (death or progressive disease) and the number of patients censored will be summarized.

Overall Survival (OS)

OS is defined as the time from the date of the first dose 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.

The analysis of OS will be based on the response-evaluable analysis set by escalation cohort, overall for dose escalation phase, and will be based on response-evaluable analysis set by expansion cohort, and overall in expansion phase. The Kaplan-Meier method will be used to estimate the distribution of OS. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method, and Kaplan-Meier OS probability estimates with 95% CIs at 3, 6 and 12 months (or later time points if data permits) will be presented. The number of patients with events and the number of patients censored will be summarized.

Sensitivity analyses for ORR, TTP, PFS and OS may be considered based on Phase 2 efficacy analysis set.

In addition to the tabulation of the analysis results, swimmer plots will be used to display the treatment course, response and duration of response; waterfall plots and spider plots will be used to display tumor size assessments and size change over the time. These plots will be produced for dose escalation phase as needed, as well as for expansion phase for each cohort and overall Phase 2 population.

7.7.3 Additional Efficacy Endpoint(s)

Best Overall Response (BOR)

Best overall response (BOR) will be explored by RECIST v 1.1 and iRECIST.

Best overall response is defined as the best response recorded after the first dose of study drug until subsequent anti-cancer therapy or EOT, whichever occur first. Responses assessed after disease progression will not be considered in determination of the best overall response.

Best overall responses ordered from best to worst are as follows: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

Confirmation of the response for solid tumor will follow guideline specified in RECIST 1.1 and iRECIST criteria. Table 7.a and Table 7.b [3,4,5] summarize some examples for BOR derivation by RECIST 1.1 and iRECIST. When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, i.e., minimum of 6-8 weeks.

Table 7.a Examples of best confirmed response derivation by RECIST v 1.1

Pattern	Best Confirmed Response
CR-PD	SD
PR-PD	SD
SD-PD	SD
CR-CR	CR
CR-NE-CR	CR
CR-SD-CR	SD
CR-NE-NE-CR	CR
PR-PR	PR
PR-CR	PR
PR-NE-PR	PR
PR-NE-CR	PR
PR-SD-PR	PR
PR-SD-CR	PR
PR-NE-NE-PR	PR
PR-SD-SD-PR	PR
PR-NE-SD-PR	PR
PR-SD-NE-PR	PR
PR-NE-NE-CR	PR
PR-SD-SD-CR	PR
PR-NE-SD-CR	PR
PR-SD-NE-CR	PR
CR-PR	SD, PD, PR
CR-SD	SD
CR-PR-PR	PR

Table 7.b Examples of best confirmed response derivation by iRECIST

Pattern	Immune-Best Overall Response
iCR-iUPD-iUPD-iCPD	iCR
iCR-iCR-iCR-iUDP-iCPD	iCR
iUPD-iPR-iCR-iCR	iCR

Table 7.b Examples of best confirmed response derivation by iRECIST

Pattern	Immune-Best Overall Response
iUPD-iSD-iCR-iCR	iCR
iUPD-iPR-iSD-iUPD	iPR
iUPD-iPR-iSD-iUPD-iCPD	iPR
iUPD-iPR-iSD-iPR-iSD	iPR
iUPD-iSD-iPR-iUPD	iPR
iUPD-NE-iPR-iUPD-NE	iPR
iUPD-iSD-iSD-iUPD-iCPD	iSD
iUPD-iSD-iUPD-NE-iUPD	iSD
iUPD-iCPD-(Any)-(Any)-(Any)	iCPD
iUPD-iUPD-iCPD-(Any)-(Any)	iCPD
iUPD-NE-NE-NE	iUPD

Some special considerations when deriving the confirmed BOR:

- Missing scans are ignored in determination of confirmed BOR. NE and missing are equivalent (e.g. for CR-NE-CR, the confirmed BOR is confirmed CR)
- SD and NE are equivalent in confirmation of PR but not for CR.

It should be noted that Table 7.a and Table 7.b only illustrate some examples, which were not intended to include all possible scenarios; for detailed information on deriving BOR, please refer to SAP.

Duration of SD (DOSD)

Duration of SD (DOSD) will be summarized for the patients with SD only as BOR.

DOSD is the time from the date of first study drug administration to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment.

DOSD (months) = (date of PD – date of first dose + 1)/30.4375.

The Kaplan-Meier method will be used to estimate the distribution of DOSD when data allows. The 25th, 50th (median), and 75th percentiles, and the corresponding 2-sided 95% confidence intervals (CIs) based on Brookmeyer and Crowley method will be presented. The number of patients with events and the number of patients censored will be summarized.

7.8 Pharmacokinetic/Pharmacodynamic Analysis

7.8.1 Pharmacokinetic (PK) Analysis

The PK of TAK-981 will be characterized in this study (ie, Pembrolizumab PK will not be characterized).

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

- Maximum observed concentration (C_{max}).
- Time of first occurrence of C_{max} (t_{max}).
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).
- Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{0-last}).
- Terminal disposition phase half-life ($T_{1/2z}$).
- Clearance (CL).
- Volume of distribution at steady state (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 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.

7.8.2 Pharmacodynamic Analysis

The analysis of tumor and blood biomarker profiles for each dose and timepoint tested will be presented in listings and will be tabulated. When possible, the dynamic range for each biomarker and fold change will be determined to better understand TAK-981 biological activity range and duration of pharmacodynamic effect in the presence of pembrolizumab, and help to determine the PAD/RP2D for the TAK-981/pembrolizumab combination. In addition, candidate response biomarkers will be evaluated and further exploratory analyses may be carried out based on emerging scientific knowledge in which case detailed statistical methods will be specified in a separate biomarker analysis plan.

7.9 Other Outcomes

7.9.1 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 analysis may be performed on an ongoing basis to assess the appropriateness of dose and 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) such as: target engagement (adduct formation), SUMO2/3 inhibition, activation of type 1 IFN response genes and cytokines/chemokines secretion in circulation.
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/schedule of TAK-981 in combination with pembrolizumab.

In addition, the 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/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.

7.10 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 population.

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

7.10.1 Dose Limiting Toxicities (DLTs)

The incidence of DLTs will be tabulated for each dose group. In addition, to assess the relationship between toxicities and TAK-981 doses, the preferred term of individual toxicities will be summarized by frequency and intensity for each dose group.

A by-subject listing of DLTs which occur during the treatment will be presented by schedule and dose level for all subjects enrolled during the dose escalation portion of this study. Subjects will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

The DLT-evaluable analysis set will be used for the analysis of DLT.

7.10.2 Adverse Events

7.10.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented in a by-patient listing. Treatment-emergent AEs are AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

Adverse events will be tabulated according to MedDRA by system organ class, high level term, and preferred term and will include the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- Incidence density of Treatment-emergent AEs.
- Maximum severity treatment-emergent AEs by all grades and Grade ≥3.
- The most commonly reported treatment-emergent AEs.
- The most commonly reported Grade 3 or higher treatment-emergent AEs.
- The most commonly reported Grade 3 or higher Drug-related treatment-emergent AEs.
- SAEs (related and regardless of relationship)
- AESIs
- Treatment-emergent AEs leading to study drug modification and discontinuation.

Patients with the same AE more than once will have that event counted only once within each body system, once within each high-level term, and once within each preferred term.

Treatment-emergent AEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each high-level term, and once within each preferred term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of any treatment arm) will be tabulated by preferred term. Patients with the same AE more than once will have that event counted only once within each preferred term.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation of study drug, and on-study deaths.

An overall summary of AESIs will be provided in the same manner as overall AE table. The number and percentage of patients with at least one AESI will be also be summarized by preferred term.

In addition, TEAEs will be summarized by each dose group.

By-patient listing of grade 3 or higher treatment-emergent AE will also be provided, where the cycle day information for the AE onset and end dates will be included in the listing.

7.10.2.2 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

7.10.2.3 Adverse Events of Special Interest

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

An overall summary of AESIs will include numbers and percentages of patients who had any AESI, drug-related AESI, grade 3 or higher AESI, grade 3 or higher drug-related AESI, serious AESI, drug-related AESI, AESI resulting in discontinuation,

The number and percentage of subjects experiencing at least 1 AESI will be summarized by MedDRA primary system organ class, high-level term, and preferred term. Drug-related AESIs will be summarized similarly.

In addition, a by-subject listing of the AESIs will be presented.

7.10.2.4 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

7.10.2.5 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

7.10.3 Clinical Laboratory Evaluations

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

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratories will be used only when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The actual values of laboratory test results and percent change from baseline will be summarized according to the scheduled sample collection time point by dose escalation cohort, overall for dose escalation phase, safety expansion cohort and overall. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE v 5.0 for toxicity from baseline to post baseline worst on study CTCAE grade, if available.

Parameters to be tabulated are included in Table 7.c and Table 7.d. In addition, shift table will also be constructed for immunosafety markers to tabulate changes in baseline categories (below normal range, within normal range, above normal range) to post baseline worst on study categories (below normal range, within normal range, above normal range).

Table 7.c Chemistry, Hematology and Coagulation 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 (CO2)	
	Creatinine	
	(Standard) C Reactive protein	
	Chloride	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Protein (total)	
	Urate	

ANC: absolute neutrophil count.

Table 7.d Clinical Urinalysis Tests

Urinalysis
Turbidity
Color
pH
Specific Gravity
Protein
Glucose
Ketones
Occult Blood
Leukocyte Esterase
Bilirubin
Nitrite
Urobilinogen
Leukocytes
Erythrocytes
Bacteria
Casts
Crystals

By-patient listings to be presented include hematology, clinical chemistry, clinically significant laboratory values, etc.

Mean laboratory values over time will be plotted for key lab parameters, including hemoglobin, leukocytes with differential, platelet count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, and standard C-reactive protein. The analysis for other lab parameters may be performed as needed.

7.10.4 Immunosafety Markers

Blood samples for the analysis of autoimmune endocrinopathies as shown in Table 7.e. They will be performed locally only. Results may be evaluated after dosing.

Table 7.e Immunosafety Determinations in Serum

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

7.10.5 Vital Signs

The actual values of vital sign parameters (blood pressure and heart rate) and weight will be summarized over time by escalation cohort and overall in dose escalation phase, by safety

expansion cohort and overall in safety expansion phase, and overall. Change of vital signs from baseline values will also be summarized over time. Vital sign values will also be presented in a by-patient listing.

The number and percentage of patients with clinically significant vital sign measurements will be tabulated as appropriate.

7.10.6 12-Lead ECGs

Descriptive statistics for the actual values and changes from values at baseline in Electrocardiograms (ECGs) will be listed by time point.

QTc interval will be calculated using Bazett's correction and Fridericia's correction, if necessary. The formulas are:

$$QTc\ (Bazett) = QT / (RR^{1/2})$$

$$QTc\ (Fridericia) = QT / (RR^{1/3})$$

where RR = 60 / heart rate (bpm)

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

ECGs abnormalities will be presented in a data listing.

7.10.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Group Performance Status and shifts from baseline to poststudy entry assessment over time, and ECOG score frequency table over time will be summarized. Shifts from baseline to the worst poststudy entry score will be tabulated by treatment arm.

7.10.8 Other Safety Parameters

Other safety parameters (including PET scan results, ECHO and MUGA, tumor prognostic markers) and change from baseline to poststudy entry assessment over time may be summarized as applicable.

7.11 Interim Analysis

Not applicable

8.0 REFERENCES

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8.1 Changes in the Statistical Analysis Plan

Revision of Cohorts

Cohort F now includes two cohorts in CPI refractory NSCLC. Cohorts G and H are removed from study.

Update Analysis Sets

The Response-Evaluable and Phase 2 Efficacy Analysis set definitions have been updated to clarify that only patients that were eligible for the study will be included. As the primary objective of the Phase 2 portion of the study is to evaluate efficacy in relatively small cohorts (Stage 1 sample sizes all ≤11 patients), it is critical for the accuracy of these evaluations that they are performed on patient populations that meet all protocol defined eligibility criteria, ensuring they are as homogenous as possible for preliminary efficacy determination. Patients that do not meet the eligibility criteria may represent different patient populations not defined by the protocol and introduce additional variables that can confound the outcomes of the efficacy analyses.

Updated Response-Evaluable and Phase 2 Efficacy Analysis set definitions are as follows:

- **Response-evaluable analysis set**: Patients who met all inclusion criteria and none of the exclusion criteria, have received at least 1 dose of study drug, have sites of measurable disease at baseline, and 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 met all inclusion criteria and none of the exclusion criteria, have received at least 1 dose of study drug in Phase 2 portion will be included in the Phase 2 efficacy analysis.

The primary efficacy analysis will be based on the Phase 2 response-evaluable analysis set. Sensitivity analyses for ORR, TTP, PFS and OS may be considered based on Phase 2 efficacy analysis set.

Study Termination

A business decision has been made to early terminate this study. Reduced scope of analysis will be included and described in the Clinical Study Report, as appropriate.