Statistical Analysis Plan

NCT Number: NCT04879849

Title: An Open-label, Phase 1, Dose-escalation Study to Evaluate the Safety and Preliminary Antitumor Activity of TAK-676 With Pembrolizumab Following Radiation Therapy in the Treatment of Non-small-cell Lung Cancer, Triple-negative Breast Cancer, or Squamous-cell Carcinoma of the Head and Neck That Has Progressed on Checkpoint Inhibitors

Study Number: TAK-676-1003

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-676-1003

An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety and Preliminary Antitumor Activity of TAK-676 With Pembrolizumab Following Radiation Therapy in the Treatment of Non–Small-Cell Lung Cancer, Triple-Negative Breast Cancer, or Squamous-Cell Carcinoma of the Head and Neck that Has Progressed on Checkpoint Inhibitors

PHASE 1

Version: **Final v3.0**

Date: 02 May 2024

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Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Final v1.0	17-DEC-2020	Not Applicable
Final v2.0	17-JUN-2022	To make SAP consistent with Amendments 1 and 2 of the study protocol
Final v3.0	02-MAY-2024	Finalizing analysis specifics before database lock

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ANC	absolute neutrophil count
BOIN	Bayesian optimal interval
CPI	checkpoint inhibitor
CR	complete response
CSR	clinical study report
DLT	dose-limiting toxicity
DOB	date of birth
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ICF	informed consent form
LVEF	Left Ventricular Ejection Fraction
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	Multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	overall response rate
PAD	pharmacologically active dose
PD	progressive disease (disease progression)

Abbreviation	Term
PK	pharmacokinetic(s)
PR	partial response
RBC	red blood cell
RP2D	recommended phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of head and neck
SD	stable disease
SOE	schedule of events
TESAE	treatment-emergent serious adverse event
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
TTR	time to response
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objectives

The primary objective is:

- To determine the safety and tolerability of TAK-676 administered in combination with pembrolizumab following radiation therapy in patients with locally advanced or metastatic NSCLC, TNBC or SCCHN.

1.2 Secondary Objectives

The secondary objectives are:

- To determine the recommended phase 2 dose (RP2D) of TAK-676 administered in combination with pembrolizumab following radiation therapy. RP2D can be equal to or lower than the maximum tolerated dose (MTD).
- To assess the preliminary antitumor activity of TAK-676 administered in combination with pembrolizumab following radiation therapy, both locally (in the radiation field) and systemically (nonirradiated lesions).
- To evaluate the dose-responsive impact on T-cell infiltration in nonirradiated tumors following TAK-676 administered in combination with pembrolizumab following radiation therapy.

1.3 Exploratory Objectives

The exploratory objectives are:

- To determine whether TAK-676 administered in combination with pembrolizumab following radiation therapy results in changes in peripheral blood consistent with activation of the innate and/or adaptive immune response.
- To characterize mutations or polymorphisms associated with response or resistance to the combination of TAK-676 and pembrolizumab following radiation therapy, for example, polymorphisms in the STING gene (TMEM173) and drug transporter genes relevant to TAK-676, and in immune response or DNA damage repair genes.
- To characterize plasma concentration of TAK-676 and explore exposure-response relationship.

2.0 STUDY DESIGN

This is an open-label, phase 1, dose escalation study to evaluate the safety, tolerability and preliminary antitumor activity of TAK-676 and pembrolizumab following radiation therapy (8 Gy × 3) in the treatment of patients with NSCLC, TNBC, or SCCHN who have progressed on CPIs. The information obtained during this study will be used to estimate the MTD and determine the RP2D of this combination.

Dose escalation of TAK-676 will follow the Bayesian Optimal Interval (BOIN) [1] design with overdose control (See Appendix E of protocol). Adequate patients will be enrolled into each cohort to achieve at least 2 DLT-evaluable patients. At least 3 patients will be enrolled in the initial cohort at the previously identified starting dose level of TAK-676 (0.2 mg). Any subsequent cohorts will initially enroll at least 2 to 3 patients. Cohorts to be explored will be identified from the TAK-676-1002 study, following dose levels that have been completed and deemed safe.

3.0 ANALYSIS ENDPOINTS

3.1 Primary Endpoints:

- Frequency and severity of treatment-emergent adverse events (TEAEs).
- Number of patients with dose-limiting toxicities (DLTs).
- Number/percentage of patients with 1 or more treatment-emergent serious adverse event (TESAE).
- Number/percentage of patients with 1 or more TEAE leading to dose modifications
- Number/percentage of patients with 1 or more TEAE leading to treatment discontinuations.

3.2 Secondary Endpoints:

Response assessments are to be made by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 [2] and also per modified itRECIST (a modified intratumoral immunotherapy Response Evaluation Criteria in Solid Tumors where intratumoral therapy references are largely replaced with radiation therapy) [3].

Response assessments per RECIST v 1.1 by investigator:

- Overall response rate (ORR): confirmed complete response (cCR) + confirmed partial response (cPR).
- Duration of response (DOR) for all tumor lesions assessed by RECIST v.1.1
- Time to response (TTR) for all tumor lesions assessed by RECIST v.1.1

Response assessments per modified itRECIST by investigator:

- ORR: cCR + cPR.
- Overall response rate for tumors lying within the radiation field (ORRirradiated): confirmed complete response (cCRirradiated) + confirmed partial response (cPRirradiated) of tumor lesions lying within the radiation field.
- Overall response rate for tumors lying outside the radiation field (ORRnonirradiated): confirmed complete response (cCRnonirradiated) + confirmed partial response (cPRnonirradiated) of tumor lesions lying outside of the radiation field.
- DOR for tumors lying within the radiation field (DORirradiated), and for those lying outside of the radiation field (DORnonirradiated).
- TTR for tumors lying within the radiation field (TTRirradiated), and for those lying outside of the radiation field (TTRnonirradiated).
- The following endpoint will be assessed to evaluate T-cell infiltration into the tumor between pretreatment and on-treatment biopsies: Cell infiltration evaluated by immunohistochemistry.

3.3 Exploratory Endpoints:

- Changes in levels of plasma biomarkers, including cytokines and chemokines.
- Changes between pretreatment and on-treatment peripheral blood samples in gene expression, including the STING agonism/type I IFN signature.
- Plasma concentrations of TAK-676.
- Relationship between response and polymorphisms in the STING gene (TMEM173) or drug transporter genes relevant to TAK-676.
- Relationship between response and mutations or polymorphisms in immune response or DNA damage repair genes. This endpoint will no longer be evaluated.

4.0 DETERMINATION OF SAMPLE SIZE

Approximately 65 patients with metastatic NSCLC, TNBC, or SCCHN will be enrolled in this study to achieve a maximum of approximately 55 DLT evaluable patients. All patients will receive radiation therapy followed by pembrolizumab administered at 200 mg IV every 3 weeks, and TAK-676 administered in a dose escalating fashion following a BOIN design, with initial explorable dose range of 0.2 to 9.0 mg administered on Days 1, 8, and 15 of every 21-day cycle. The sample size of 55 DLT evaluable patients was based on the 11 explorable dose levels from 0.2 to 9.0mg. At study end, 34 patients were enrolled with 32 receiving at least one dose of TAK-676 ranging from 0.2mg to 5.0mg.

5.0 METHODS OF ANALYSIS AND PRESENTATION

5.1 General Principles

No formal statistical hypothesis testing will be performed. In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables; additionally, the first and third quartiles may be reported. For categorical data, the number and percent of non-missing values per category will be displayed. The mean, median, first quartile, and third quartile will be presented to 1 more decimal place than the recorded data. Standard deviations will be presented to 2 more decimal places than the recorded data. The minimum and maximum will be presented using the same number of decimal places as the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

All 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 prior to the first dose of radiation, which, for most assessments, corresponds to the screening values.

The summary tables will include each dose cohort and overall.

Screen failure patients will be grouped and listed.

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

5.1.1 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of study drugs (TAK-676 or pembrolizumab). Other study days are defined relative to Study Day 1 with day 1 being Study Day 1 and day -1 being the day prior to Study Day 1. The radiation therapy will be given on Days -8 to -2. If TAK-676 and pembrolizumab treatment date data are not available, -8 will be used as the initial radiation exposure study day and the following two radiation days (if radiation exposure continues) will then be between -7 and -2.

5.1.2 Definition of Study Visit Windows

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

5.1.3 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, assuming 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.

5.1.4 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 the 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 are missing, then it is imputed with 1st dose date.

Imputing missing AE start dates 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. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the 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.

If patient 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.

5.1.5 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 are 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 dates of concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If a patient dies, then use the death date for the concomitant therapy's stop date. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur

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

5.1.6 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.

5.2 Analysis Sets

The Analysis Sets (Analysis Populations) will include the following:

- **Safety analysis set**: Patients who have received at least 1 dose of radiation will be included in all safety analyses.
- **PK analysis set**: Patients dosed with TAK-676 for whom plasma concentration data have been collected will be used for PK analyses. In addition to patients having follow-up data, patients having only baseline plasma concentration data will be included in this analysis set.
- **DLT-evaluable analysis set**: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-676, pembrolizumab, and three doses of radiation without experiencing a DLT by the end of Cycle 1 follow-up and patients who receive three doses of radiation, pembrolizumab, and the required TAK-676 doses up until a DLT during Cycle 1.
- **Comprehensive response-evaluable analysis set**: The comprehensive response-evaluable analysis set, a subset of the safety analysis set, includes patients with measurable disease at baseline and at least 1 posttreatment evaluation or who discontinued before their first postbaseline tumor assessment.

- **Response-evaluable analysis subset:** The response-evaluable analysis subset, a subset of the comprehensive response evaluable analysis set, will include patients with measurable disease at baseline and at least 1 posttreatment evaluation.
- **Pharmacodynamic analysis set**: The pharmacodynamic analysis set will include those patients in the safety analysis set who have received at least 1 dose of TAK-676 and who have baseline and at least 1 postbaseline pharmacodynamic sample assessment (defined as a timepoint where the pharmacodynamic measurements outlined in 9.4.15.3 [Biomarker and Pharmacodynamic Measurements] of the protocol are collected; see the SOE in protocol for the specific timeline).

The number of patients in the safety, pharmacokinetics, DLT-evaluable, comprehensive response-evaluable, response-evaluable, and pharmacodynamic analysis sets will also be summarized. Patients ineligible to participate in the study who were, regardless, exposed to any study treatment, will be excluded from all analysis sets other than the safety analysis set.

5.3 Disposition of Patients

Dispositions of patients will be presented by dose level, and if deemed useful, by disease indication, for patients in the safety analysis set. 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 analysis set. A listing will present data concerning patient disposition.

5.4 Demographic and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively by dose level and overall. Variables to be analyzed include sex, age, race, ethnicity, height, weight, prior medications/therapies, 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.

Demographic data will also be presented in a by-patient listing. Age will be calculated from date of birth to date of informed consent. No inferential statistics will be generated.

Baseline characteristics assessments include but may not be limited to: disease primary diagnosis, years since initial diagnosis, histologic type and grade, PD-L1 status tested, PD-L1 test used, PD-L1 score, and Eastern Cooperative Oncology Group (ECOG) performance status.

A separate table will summarize the numbers and percentages of patients who received prior therapy, including prior anticancer and median number of prior anticancer therapies, prior therapy specifically with a Checkpoint Inhibitor (broken down by anti-PD1, anti-PD-L1 and anti-CTLA4 agents), prior radiation, prior surgery, and best response to the last prior anticancer therapy.

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

5.5 Medical History, Concurrent Medical Conditions and Concomitant Medications

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

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 the WHO drug generic term for the safety analysis set, from first dose of radiation 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.

5.6 Study Drug Exposure and Compliance

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

Extent of Exposure:
The exposure to TAK-676 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, ≥4, ≥5, ≥6, ≥7, and ≥8 treated cycles for patients in the safety analysis set. 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 percentage of patients who had ≥3, ≥6, … weeks of treatment will be summarized for patients in the safety analysis set. The period of radiation therapy will be excluded from the calculation.

Amount of dose taken (mg) is defined as (treatment vehicle amount administered/vehicle amount prepared) x prepared dose. Relative dose intensity (RDI) (%) will be presented overall and by cycle. Overall RDI is defined as 100 x (total dose received in mg) / (initial prescribed dose per cycle x number of treated cycles). Cycle RDI is defined as 100 x (total dose received in mg in cycle) / (initial prescribed dose per cycle). Initial prescribed dose is the dose level to which a patient is originally assigned at study onset. If a patient's dose level is reduced, the initial prescribed dose at study onset will still be used in the above RDI equations.

The extent of exposure will be summarized by dose level and overall.

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

Action on Drug:
Actions on study drug (e.g., dose reduced due to AE) will be summarized by cycles and total for each dose level and overall. Aggregate summary such as by cycles 1-3, 4-6, and 7+ may also be provided if deemed appropriate.

Radiation Therapy Exposure:

Radiation therapy exposure data will be summarized by dose level and overall. The following information will be summarized: actual radiation dose received, number of distinct anatomic sites

irradiated, number of patients not receiving the full planned radiation dose and their reasons. The same data will also be presented in a by-patient listing, which will also display the actual anatomic sites irradiated for each patient.

5.7 Efficacy Analysis

Efficacy is not the primary endpoint for this study. Secondary efficacy endpoints include ORR, ORRnonirradiated, ORRirradiated, DOR, DORnonirradiated, DORirradiated, TTR, TTRnonirradiated and TTRirradiated. No formal statistical tests will be performed for these secondary endpoints. Instead, they will be summarized descriptively for each dose level and overall.

5.7.1 Primary Efficacy Endpoint(s)

There are no primary efficacy endpoints for the study.

5.7.2 Secondary Efficacy Endpoint(s)

Response assessments are based on RECIST v.1.1 [2] and modified itRECIST [3] (see Figure 5.1) by investigator at each timepoint and the best overall response for each patient will be derived programmatically from the reported responses. RECIST v.1.1 will exclude radiated lesions from consideration (see protocol for detailed explanation). The algorithm for confirmed CR and PR (cCR and cPR) is described in Appendix 7.2.

We have also defined efficacy endpoints specifically for two subgroups of lesions: irradiated (local) and nonirradiated (abscopal). Both irradiated and nonirradiated responses will be assessed based on the totality of the irradiated and nonirradiated lesions respectively, using the previously specified target lesions for the sum of largest diameters as well as previously specified non-target lesions as indicated by RECIST v1.1 and modified itRECIST. Target and non-target lesions are assigned prior to radiation per RECIST v1.1 and modified itRECIST criteria and remain unchanged when assessing irradiated and nonirradiated responses. For each patient at each lesion response assessment, the sum of the longest diameters (LD) of the target lesions will be reported in addition to the percentage change when compared to the baseline sum of the LD of the target lesions and the nadir sum of the LD of the target lesions. The nadir sum is defined as the smallest sum of the LD of the target lesions recorded previous to the timepoint being assessed (including baseline). All below secondary efficacy endpoints will be analyzed using the response-evaluable analysis subset except for ORR, ORRnonirradiated, and ORRirradiated, which will also be analyzed using the comprehensive response-evaluable analysis set.

ORR is defined as the proportion of patients who achieve cCR or cPR (determined by the investigator) during the study.

ORRnonirradiated is defined as the proportion of patients who achieve cCR or cPR (determined by the investigator) in the tumor lesions lying outside of the radiation field during the study.

ORRirradiated is defined as the proportion of patients who achieve cCR or cPR (determined by the investigator) in the tumor lesions lying within the radiation field during the study.

DOR is the time from the date of first documentation of a cPR or better per RECIST 1.1 criteria to the date of first documentation of PD or death for responders (cPR or better). Responders without documentation of PD will be censored at the date of last response assessment that is SD or better. Censoring rules for DOR are defined in Appendix 7.3.

DORnonirradiated is the time from the date of first documentation of a cPR or better in the tumor lesions lying outside of the radiation field to the date of first documentation of nonirradiated PD in those lesions or death for nonirradiated responders (cPR or better). Nonirradiated responders without documentation of nonirradiated PD will be censored at the date of last response assessment that is nonirradiated SD or better. Censoring rules for DORnonirradiated are defined in Appendix 7.3.

DORirradiated is the time from the date of first documentation of a cPR or better in the tumor lesions lying within the radiation field to the date of first documentation of irradiated PD in those lesions or death for irradiated responders (cPR or better). Irradiated responders without documentation of irradiated PD will be censored at the date of last response assessment that is irradiated SD or better. Censoring rules for DORirradiated are defined in Appendix 7.3.

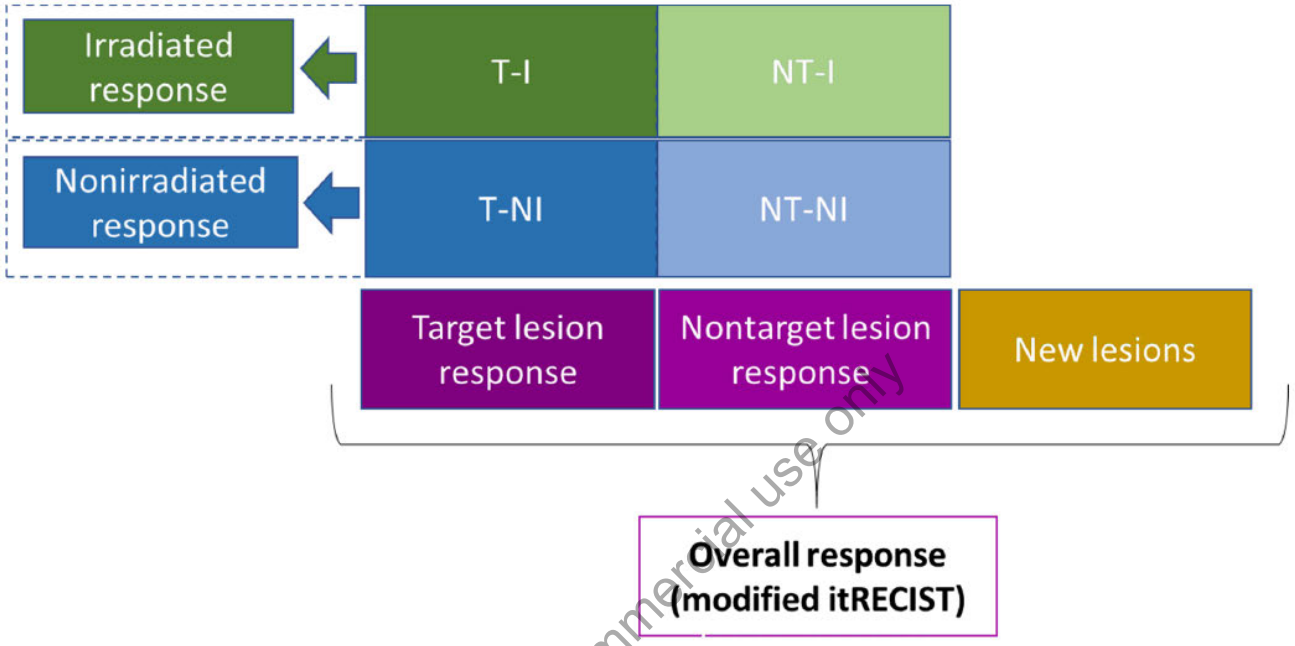
TTR is defined as the time from the date of first dose administration of TAK-676 to the date of first documented cPR or better per RECIST 1.1 criteria by the investigator.

TTRnonirradiated is defined as the time from the date of first dose administration of TAK-676 to the date of first documented cPR or better in the tumor lesions lying outside of the radiation field by the investigator.

TTRirradiated is defined as the time from the date of first dose administration of TAK-676 to the date of first documented cPR or better in the tumor lesions lying within the radiation field by the investigator.

ORR, ORRnonirradiated and ORRirradiated will be summarized using descriptive statistics with 95% confidence intervals. DOR, DORnonirradiated, DORirradiated, TTR, TTRnonirradiated and TTRirradiated will be analyzed using the Kaplan-Meier method.

Figure 5.1 Illustration of Irradiated, Nonirradiated, and Overall Responses



TI: target irradiated; T-NI: target nonirradiated; NT-I: nontarget irradiated; NT-NI: nontarget nonirradiated [3]

5.8 Pharmacokinetic/Pharmacodynamic Analysis

5.8.1 Pharmacokinetic (PK) Analysis

Individual TAK-676 concentration-time data 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. A value of zero will be assigned for any assay result below the lower limit of quantification (BLQ) when computing summary statistics.

The PK data collected in this study are intended to contribute to future population PK analyses of TAK-676. These population PK analyses may additionally include data collected in other TAK-676 clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

5.8.2 Pharmacodynamic (PD) Analysis

Changes between pretreatment and on-treatment peripheral blood samples in immune cell subsets, including their frequency, activation state, and clonality, changes in levels of plasma cytokines and

chemokines and in gene expression in blood cells, and changes between screening and on-treatment tumor biopsies in immune contexture, protein expression, and gene expression may be summarized.

The relationship between response to combination treatment regimen and mutations or polymorphisms in immune response or DNA damage repair genes may be analyzed. The relationship between response to combination treatment regimen and polymorphisms in the STING gene (TMEM173) and drug transporter genes relevant to TAK-676 may be investigated.

T-cell infiltration into the tumor as measured by immunohistochemistry is a secondary endpoint and its change from pre-treatment to on-treatment biopsies will be evaluated. Based on a literature survey (see Appendix K of the Protocol), we assumed a geometric mean for a 2.5-fold increase and a coefficient of variation of 130% and projected that a minimum of 11 pairs of high quality and interpretable biopsies are needed to demonstrate a 0.8 posterior probability of achieving a 1.5-fold increase in Bayesian analysis with an 80% probability of success. In order to achieve the 11 biopsy pairs, more than 11 patients will need to be biopsied within an indication depending on the biopsy quality and interpretability. Assuming 60%, 70% and 80% success rate of each biopsy and the independence of quality between pre-treatment and on-treatment biopsies, the number of biopsied patients needed are 31, 22 and 17. This Bayesian analysis of the paired biopsies was to be planned once an indication-specific expansion cohort was built into the study, however it has been decided that the study will close-out without including expansion cohorts.

Analysis will be performed in the pharmacodynamic analysis set.

5.9 Other Outcomes

5.9.1 PK/ Pharmacodynamic Analysis

The relationship between TAK-676 plasma exposure and pharmacodynamic response (eg, degree of immune activation, changes in cytokines/chemokines, gene expression changes) will be explored on an ongoing basis as PK and pharmacodynamic data become available to understand the PK/pharmacodynamic relationship of TAK-676. Data permitting, mathematical models may be used to describe this relationship, and such models may be used to predict the dose/schedule of TAK-676 that provides the desired exposure and pharmacological response for future evaluation. These data may be presented graphically as well as summarized in the CSR. The analysis will be performed in the pharmacodynamic analysis set if enough PK data are available to allow for an informative investigation.

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-676. 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 CSR for this study but will be presented in a separate report.

5.10 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 analysis set.

5.10.1 Dose Limiting Toxicities (DLTs)

The incidence of DLTs will be tabulated for each dose level in the DLT-evaluable analysis set. In addition, to assess the relationship between toxicities and TAK-676 doses, the preferred term of individual toxicities will be summarized by frequency and intensity for each dose level.

A by-patient listing of DLTs will be presented by dose level. Patients will be grouped by the dose level to which they were originally assigned.

5.10.2 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. Causality between each AE and the study drugs will be indicated in this listing and all the other AE listings specified in this SAP.

Treatment-emergent AEs are AEs that occur after administration of the first dose of any study drug (defined as TAK-676, pembrolizumab, or radiation therapy) and through 30 days after the last dose of any study drug, except for an immune-mediated AE. An immune-mediated AE will be considered as treatment-emergent if it occurs after administration of the first dose of study drug and through 90 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).

Related immune-mediated AEs as determined by the investigator that occur after administration of the first dose of any study drug and through 90 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) will be tabulated and treated as a subgroup of the treatment-emergent AEs. Additionally, the occurrence of and results from the 90-day safety check will be included in the listings.

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

- Treatment-emergent AEs (treatment is defined as radiation, pembrolizumab, or TAK-676 exposure)
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs

- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥10% of all patients)
- Treatment-emergent SAEs (related and regardless of relationship)
- 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, and once within each preferred term. Details for each category are described below.

5.10.2.1 Treatment-emergent Adverse Events

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

The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥ 10% of all patients) 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 of 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, and grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation, treatment-emergent AE resulting in study drug modification and on-study deaths.

In addition, TEAEs will be summarized by dose level and overall.

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.

By-patient listing of all 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.

5.10.2.2 Serious Adverse Events

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

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

5.10.2.3 Deaths

Summary of TEAEs resulting in death will be summarized. Death will be summarized by on-study death and follow-up death. On-study death is defined as a death that occurs between the first dose of radiation and up to and including 30 days from the last dose of any study drug or radiation unless the death is due to a related immune mediated AE through 90 days after the last dose of any study drug or radiation. Follow-up death is defined as the death that occurs after 30 days of the last dose of any study drug.

A by-patient listing of all deaths will be presented.

5.10.2.4 Adverse Events Resulting in Modification and Discontinuation of Study Drug

The number and percentage of treatment-emergent AEs resulting in study drug modification and discontinuation will be summarized by dose levels and overall.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented.

5.10.3 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 lab value is reported using a non-numeric qualifier [e.g., less than (<) a certain value, or greater than (>) a certain value], the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

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

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 and overall. Laboratory data will also be presented in listings.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity from baseline to post baseline worst on study CTCAE grade, if available. Parameters to be tabulated are included in Table 5.1:

Table 5.1: Clinical Chemistry, Hematology, Coagulation, Thyroid Function and Urinalysis Tests

Hematology	**Serum Chemistry**	
Hematocrit	Protein (total)	Magnesium
Hemoglobin	Albumin	Phosphate
Leukocytes with differential	Alkaline phosphatase	Potassium
Neutrophils (ANC)	Alanine aminotransferase	Sodium
Platelets (count)	Aspartate aminotransferase	Chloride
RBC	Bilirubin (total)	Urate
MCH	D-Bilirubin	
MCV	Gamma glutamyl transferase	
MCHC	Glucose (random blood glucose)	
	Lactate dehydrogenase	
	Amylase	
	Lipase	
	Calcium	
	Bicarbonate (if available as a part of blood chemistry panel of local laboratory)	
	C-reactive protein	
	Blood urea nitrogen	
	Creatinine	
Thyroid Function	**Coagulation**	
Thyrotropin	Activated partial thromboplastin time	
Thyroxine, free (T4)	Prothrombin time (or prothrombin international normalized ratio)	
Total or free triiodothyronine (total or free T3)		
Urinalysis Tests	**Other**	
Bilirubin	Ferritin	
Glucose	Creatine phosphokinase	
Ketones		
Leukocytes		
Nitrite		
Occult blood		
pH		

Protein Specific gravity Turbidity and color Urobilinogen	

ANC: absolute neutrophil count; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cell.

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

Mean laboratory values over time may be plotted for key lab and safety parameters; values may be stratified by disease indication if deemed useful.

5.10.4 Vital Signs

The actual values of vital sign parameters (blood pressure, heart rate, respiratory rate, oxygen saturation and temperature) and weight will be summarized over time by dose level and overall. If vital signs are collected multiple times within a day, all of them will be reported. 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.

5.10.5 Safety ECGs

ECG intervals (QT, QTcF, PR, QRS and heart rate) will be summarized at each scheduled time point, along with mean change from baseline to each post-treatment time point.

The formula for calculating Fridericia's rate-corrected QT intervals (QTcF) are below:

$$QTcF = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (< 450 msec, 450-480 msec, > 480- <500 msec, and ≥ 500msec) will be summarized at 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 QTcF intervals and maximum changes from study entry will also be summarized similarly in a separate display.

All ECG data will be presented in a by-patient listing. All ECGs abnormalities will also be presented in a data listing.

5.10.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Group Performance Status and shifts from study entry to post study entry assessment over time and ECOG score frequency over time will be summarized. Shifts from study entry to the worst post study entry score will be tabulated by dose level and overall.

5.10.7 Other Observations Related to Safety

The assessment of LVEF measured by echocardiography or MUGA will be performed at screening and as clinically indicated. Any findings from LVEF determinations will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

5.11 Protocol Deviations

All significant protocol deviations will be presented in a listing.

5.12 Interim Analysis and Criteria for Early Termination

Although no formal interim analysis is planned, investigators and sponsor representatives will review accruing data at end-of-cohort meetings to determine dose escalation and the number of patients per cohort.

5.13 Stopping Rules

The study will be stopped if 2 fatal AEs related to TAK-676 and/or pembrolizumab occur at the same dose level in Cycles 1 and 2. The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients, depending on the nature and severity of the safety risk. A final decision to terminate the study or a protocol amendment will be made only after a full review of the safety data by the sponsor's Safety Management Team and the investigators. Based on the emerging safety profile, alternative rules may also be considered following discussions between the sponsor and the investigators.

5.14 Changes in the Statistical Analysis Plan

To be updated as needed.

6.0 REFERENCES

1. Liu S, Yuan Y. Bayesian Optimal Interval Designs for Phase I Clinical Trials. J R Stat Soc Ser C Appl Stat 2015;64(3):507-23.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
3. Goldmacher, G. V., Khilnani, A. D., Andtbacka, R. H. I., Luke, J. J., Hodi, F. S., Marabelle, A., et al. 2020. Response criteria for intratumoral immunotherapy in solid tumors: itRECIST. J Clin Oncol, 38(23), 2667-76.

7.0 APPENDIX

7.1 Changes from the Previous Version of the SAP

Changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below. For changes made from the initial SAP to v2.0, refer to v2.0.

SAP Section	Impacted Text	Change	Rationale for Change
5.1.1	None	Added text: "If TAK-676 and pembrolizumab treatment date data are not available, -8 will be used as the initial radiation exposure study day and the following two radiation days (if radiation exposure continues) will then be between -7 and -2	Add rules for the handling of radiation study day labels
5.7.2	None	Clarity added to description of secondary efficacy RECIST endpoints	Clarity of endpoints
5.8.1	None	Added text: "A value of zero will be assigned for any assay result below the lower limit of quantification (BLQ) for computing summary statistics."	Clarify handling of BLQ TAK-676 concentration-time data
7.3	None	Added table: "Censoring Rules for DOR, DORnonirradiated, and DORirradiated"	Censoring rules were added to be consistent with TAK-676-1002 and clarify handling

7.2 Summary of the Best Overall Response Status Calculation when Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point[a]	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[b]
CR	SD	SD provided minimum criteria for SD duration met[c], otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
[a] The assessment confirming a CR or PR must take place at least 4 weeks after the response of interest.
[b] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
[c] SD duration should be at least 6 weeks after administration of TAK-676.

7.3 Censoring Rules for DOR, DORnonirradiated, and DORirradiated

Situation	End Date on or prior to cut-off date	Censored
Death or documented progression without missing two or more consecutive tumor assessments	Date of documented progression or death, whichever occurs earlier	No
Documented progression after two or more consecutively missed tumor assessments	Date of last tumor assessment before the missed visits	Yes
Death before documented progression but after two or more consecutively missed tumor assessments	Date of last tumor assessment before the missed visits	Yes
Discontinued the study without documented progression and alive by the time of discontinuation	Date of last tumor assessment before discontinuation	Yes
Prohibited new anticancer treatment started prior to documented progression	Date of last tumor assessment before start of prohibited new treatment	Yes
Patients followed by tumor assessments without documented progression at data cut-off date	Date of last tumor assessment before database cutoff date	Yes

The window for consecutive tumor assessments is defined as follow:
If the last tumor assessment date in both SDTM.TR and SDTM.RS is ≤12 months from treatment start date (TAK-676), use 18 weeks + 7 days as the two consecutive responses assessment window. **Otherwise**, use 36 weeks + 7 days as the two consecutive responses assessments window.

Signature Page for TAK676-1003_SAP_3.0_02MAY2024

Title:

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