Statistical Analysis Plan

NCT Number: NCT05070247

Title: An Open-label, Dose Escalation and Expansion, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of TAK-500, a Novel Stimulator of Interferon Genes Agonist, as a Single Agent and in Combination With Pembrolizumab in Adult Patients With Select Locally Advanced or Metastatic Solid Tumors

Study Number: TAK-500-1001

Document Version and Date: Final 2.0, 20 Feb 2024

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

For non-commercial use only

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-500-1001

An Open-label, Dose Escalation and Expansion, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of TAK-500, a Novel Stimulator of Interferon Genes Agonist, as a Single Agent and in Combination with Pembrolizumab in Adult Patients with Select Locally Advanced or Metastatic Solid Tumors

Phase 1/2 Study of TAK-500 as a Single Agent and in Combination With Pembrolizumab in Patients With Select Locally Advanced or Metastatic Solid Tumors

For non-commercial use only

Version: **Final 2.0**

Date: 20 February 2024

Prepared by:

[redacted], PhD

[redacted], Statistical and Quantitative Sciences

Based on:

Protocol Version: Amendment 3

Protocol Date: 13 June 2023

CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda.

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Final v1.0	03-SEP-2021	Not Applicable
Final v2.0	20-FEB-2024	To make SAP consistent with Amendment 3 of the study protocol

For non-commercial use only

2.0 TABLE OF CONTENTS

For non-commercial use only

For non-commercial use only

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CL	total clearance after intravenous administration
C_{max}	maximum observed concentration
CR	complete response
CRS	cytokine release syndrome
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HCC	hepatocellular carcinoma
ICF	informed consent form
IFN	interferon
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
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

For non-commercial use only

Abbreviation	Term
PD	progressive disease (disease progression)
PDS	programming derivation specification
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
[redacted]	[redacted]
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Rac	accumulation ratio
RDE	recommended dose for expansion
RDI	relative dose intensity
RE	response evaluable
RECIST	response evaluation criteria in solid tumors
RO	receptor occupancy
RP2D	recommended phase 2 dose
SA	single agent
SAE	serious adverse event
SCCHN	squamous cell carcinoma of head and neck
STING	stimulator of interferon genes
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
t_{max}	first time to reach maximum (peak) plasma concentration
TME	tumor micro-environment
TNBC	triple-negative breast cancer
TTR	time to response
V_{ss}	volume of distribution at steady state after intravenous administration
WHO	World Health Organization

For non-commercial use only

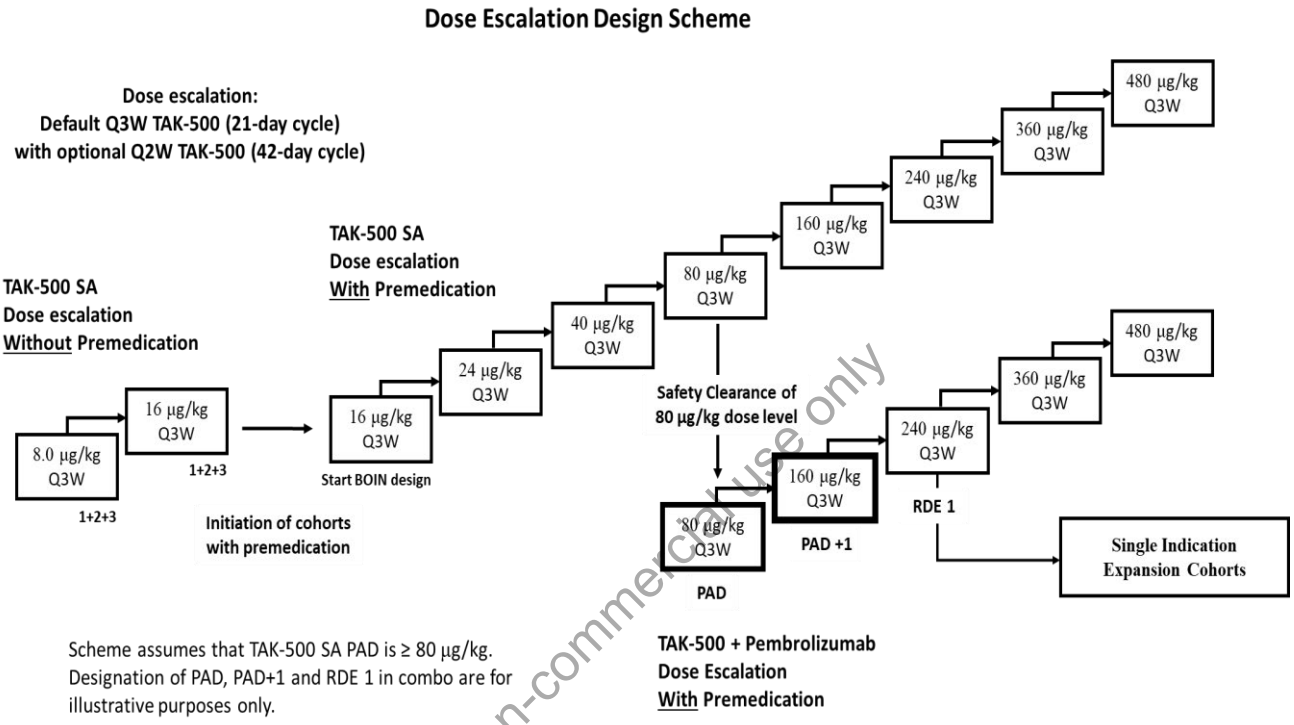
4.0 STUDY DESIGN OVERVIEW AND OBJECTIVES

4.1 Study Design Overview

TAK-500-1001 is a phase 1/2, open-label, dose escalation and expansion study designed to determine the safety, tolerability, antitumor activity, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of TAK-500, a novel Stimulator of Interferon Genes (STING) agonist, as a single agent (SA) and in combination with pembrolizumab. This information will be used to determine the pharmacologically active dose (PAD) range and the dose for further development of TAK-500 as a SA and in combination with pembrolizumab. The study will proceed in 2 main sections: (1) a phased dose escalation of each treatment arm (TAK-500 as a SA and in combination with pembrolizumab, crossover from SA to combination being allowable) as shown in Figure 4.a and (2) the evaluation of TAK-500 as a SA and in combination with pembrolizumab in single tumor type expansion cohorts (Figure 4.b). In the dose escalation, independent cohorts are defined by the dose level and specific pre-medication regimen; escalation proceeds using an initial 1+2+3 approach followed by BOIN (refer to protocol Sections 6.1.2.1-2 and Appendix F). Both dose escalation and dose expansion cohorts allow for exploration of once every 3 weeks (Q3W) versus once every 2 weeks (Q2W) administration of TAK 500. Approximately 313 patients in total will be enrolled in this study. In the dose escalation phase (phase 1), approximately 82 patients will be enrolled with the following 9 types of locally advanced or metastatic solid tumors: gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma (HCC), nonsquamous non–small cell lung cancer (NSCLC), squamous-cell carcinoma of the head and neck (SCCHN), mesothelioma, triple-negative breast cancer (TNBC), renal clear cell carcinoma (RCC), and nasopharyngeal carcinoma (NPC). In the dose expansion phase (phase 2), approximately 231 patients will be enrolled with the following 3 types of locally advanced or metastatic solid tumors: nonsquamous NSCLC, pancreatic adenocarcinoma, and RCC. Additional expansion cohorts in the same or other select tumor types may be warranted based on safety, pharmacodynamics, and clinical activity. For details of the study design, refer to Section 6 of the protocol.

For non-commercial use only

Figure 4.a Overview of Study Design – Dose Escalation (Phase 1)



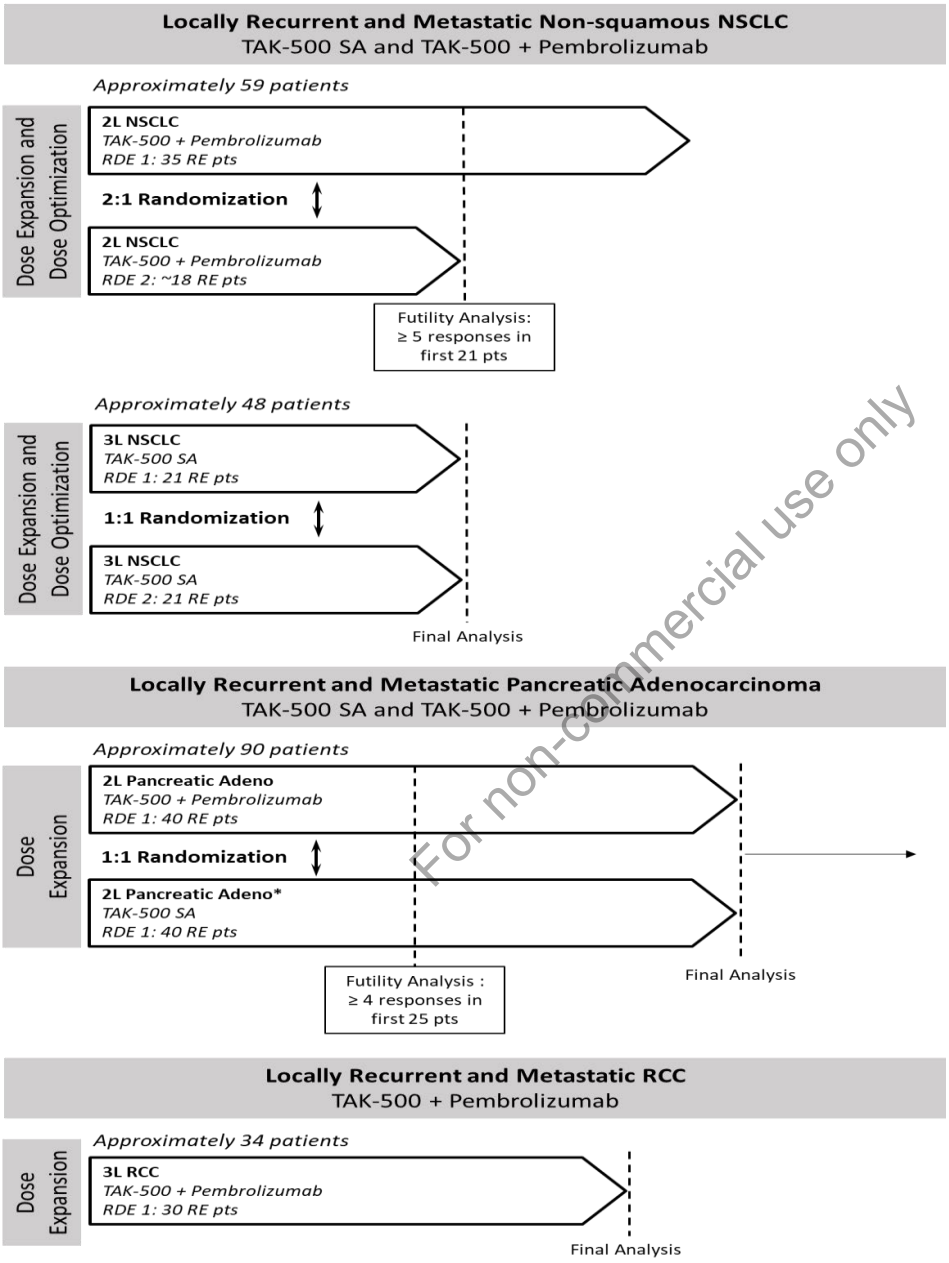
For non-commercial use only

BOIN [1]: Bayesian Optimal Interval; DL: dose level; Q2W: once every 2 weeks; Q3W: once every 3 weeks; PAD: pharmacologically active dose; RDE: recommended dose for expansion; SA: single agent.

PAD in figure refers to the minimum PAD.

Scheme assumes that TAK-500 SA PAD is ≥80 µg/kg. Designation of PAD, PAD +1, and RDE in combination are for illustrative purposes only.

Figure 4.b Overview of Study Design – Dose Expansion (Phase 2)



For non-commercial use only

2L: second-line; 3L: third-line; length of bar meant to represent relative patient numbers and not time required for a given cohort; NSCLC: non–small cell lung cancer; Pancreatic Adeno: pancreatic ductal adenocarcinoma; pts: patients; RCC: renal clear cell carcinoma; RDE: recommended dose for expansion; RE: response-evaluable; SA: single agent.

4.2 Primary Objectives

The primary objective for the phase 1 dose escalation phase is:

- To determine the safety and tolerability of TAK-500 administered as SA and in combination with pembrolizumab in patients with select locally advanced or metastatic solid tumors, including gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC

The primary objectives for the phase 2 dose expansion phase are:

- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic nonsquamous NSCLC
- To assess the preliminary antitumor activity of TAK-500 SA in 3L recurrent locally advanced or metastatic nonsquamous NSCLC
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma
- To assess the preliminary antitumor activity of TAK-500 SA in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 3L recurrent locally advanced or metastatic RCC
- To determine the dose for further development of TAK-500 administered as SA and in combination with pembrolizumab

For non-commercial use only

4.3 Secondary Objectives

The secondary objectives for the phase 1 dose escalation are:

- To determine the RDE of TAK-500 administered as SA and in combination with pembrolizumab
- To characterize the single and multiple dose PK of TAK-500 administered as SA and in combination with pembrolizumab
- To evaluate the preliminary antitumor activity of TAK-500 administered as SA and in combination with pembrolizumab
- To evaluate the dose-responsive impact on T-cell infiltration into the tumor following TAK-500 administered as SA and in combination with pembrolizumab
- To determine the immunogenicity of TAK-500

The secondary objectives for the phase 2 dose expansion are:

- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic nonsquamous NSCLC
- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic pancreatic adenocarcinoma
- To determine the safety and tolerability of TAK-500 combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic RCC

4.4 Exploratory Objectives

The exploratory objectives are:

- To assess [redacted] induced by TAK-500 as an SA and in combination with pembrolizumab in blood as evidence of pharmacodynamic modulation
- To determine whether TAK-500 as an SA and in combination with pembrolizumab results in changes in peripheral blood and/or tumor consistent with [redacted]
- To examine whether the combination of TAK-500 as an SA and in combination with pembrolizumab results in blockade of [redacted] and activation of [redacted]
- To explore relationships between serum concentrations of TAK-500, total antibody, and deconjugated TAK-676 in combination with pembrolizumab with pharmacodynamics, antitumor activity, and safety endpoints
- To assess the relationship between [redacted]
- To characterize [redacted] of TAK-500 as an SA and in combination with pembrolizumab and relationship to dose
- To characterize [redacted], including [redacted], for correlations with clinical outcome, pharmacodynamics, and PK, including future pharmacogenomic exploration of [redacted]

[redacted]

- [redacted]

For non-commercial use only

[redacted]

- [redacted]

For non-commercial use only

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints:

The primary endpoints for the phase 1 dose escalation are:

- Frequency and severity of TEAEs
- Number of patients with DLTs
- Number and percentage of patients with 1 or more treatment-emergent SAE
- Number and percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations

The primary endpoints for the phase 2 dose expansion are:

- Response assessments made by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: confirmed complete response (cCR) + confirmed partial response (cPR)

For non-commercial use only

5.2 Secondary Endpoints:

The secondary endpoints for dose escalation and dose expansion are:

- PK parameters of TAK-500:
  - C_{max}
  - t_{max}
  - Area under the serum concentration-time curve from time 0 to time t (AUC_t)
  - AUC_∞
  - Terminal disposition phase half-life ($t_{1/2z}$)
  - Total clearance after intravenous administration (CL)
  - Volume of distribution at steady state after intravenous administration (V_{ss})
- Intratumoral T-cell infiltration upon TAK-500 treatment
- Incidence of patients who are ADA-positive and have acquired immunogenicity

Additional secondary endpoints for the phase 1 dose escalation only:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: cCR + cPR
  - Disease control rate (DCR): cCR + cPR + stable disease (SD) ≥ 6 weeks (see Section 7.7.2 for explicit definition)
  - Duration of response (DOR): the time from the date of first documentation of a cPR or better to the date of first documentation of PD or death by any cause for responders (cPR or better)
  - Time to response (TTR): the time from the date of first dose administration to the date of first documented cPR or better by the investigator

Additional secondary endpoints for the phase 2 dose expansion only:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - DCR: cCR + cPR + stable disease (SD) ≥ 6 weeks (see Section 7.7.2 for explicit definition)
  - DOR: the time from the date of first documentation of a cPR or better to the date of first documentation of PD or death by any cause for responders (cPR or better)
  - TTR: the time from the date of first dose administration to the date of first documented cPR or better by the investigator
  - PFS
  - OS
- Frequency and severity of TEAEs
- Number of patients with DLTs
- Number and percentage of patients with 1 or more treatment-emergent SAE
- Number and percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations

For non-commercial use only

5.3 Exploratory Endpoints:

The exploratory endpoints include:

- Changes in [redacted] between pretreatment and on-treatment peripheral blood samples
- The following endpoints will be assessed to evaluate changes in peripheral blood and/or tumor:
  - Changes in concentrations of plasma biomarkers, including [redacted]

- Changes between pretreatment and on-treatment peripheral blood samples in [redacted]

- [redacted]
- Relationship between [redacted]
- Relationship between serum concentrations of TAK-500, total antibody, and deconjugated TAK-676 in combination with pembrolizumab with pharmacodynamics, antitumor activity, and safety endpoints
- [redacted]
- [redacted] assessed by sequencing of tumor and normal tissue

[redacted].

- [redacted]

[redacted]

- [redacted]
- [redacted]

For non-commercial use only

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 313 patients will be enrolled in the study, including approximately 82 in the dose escalation phase and approximately 231 in the dose expansion phase (assuming only 1 dose schedule will be expanded).

In the phase 1 dose escalation phase, approximately 52 patients will be enrolled to achieve about 46 DLT-evaluable patients in the SA arm, and approximately 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients in the combination arm (assuming a drop-out rate of 10%). In the SA arm, a maximum of 42 DLT-evaluable patients is planned for BOIN escalation to cover 8 dose levels and additionally 4 DLT-evaluable patients for the two 1 + 2 + 3 escalation dose levels. In the combination arm, the number of patients will depend on the starting dose level. Assuming the escalation starts at 80 µg/kg, a maximum of 27 DLT-evaluable patients will be enrolled. Additional patients may be enrolled for the evaluation of Q2W administration of TAK-500 if this schedule is explored in the dose escalation phase (in either the SA or combination arm).

In the phase 2 dose expansion phase, each cohort's sample size is based on Simon's 2-stage design or an exact binomial 1-stage design with ORR as the endpoint, a 1-sided alpha equal to 0.1, and an assumed dropout rate of 10%. In the following cohort-specific design specifications, H_0 represents the "null hypothesis," H_A represents the "alternative hypothesis," RE represents clinically-defined "response-evaluable" patients (note that this differs from statistically-defined RE patients as described in Section 7.2), and power represents "statistical power." Additionally, specific design scenarios are dependent on the results from preceding scenarios and may or may not be realized. Further details are provided in Section 6.0 of the protocol.

For non-commercial use only

- *2L NSCLC TAK-500 + pembrolizumab RDE 1 versus RDE 2 [2:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 39 patients will be enrolled in the RDE 1 cohort, allowing for 35 RE patients. H_0: ORR ≤ 23%, H_A: ORR ≥ 40%, and power = 80%. The futility analysis will occur at 21 RE patients, where ≥ 5 responders are required to continue enrollment.
  - Approximately 20 patients will be enrolled in the RDE 2 cohort, allowing for 18 RE patients. If the futility analysis in RDE 1 determines that enrollment should stop in RDE 1, additional enrollment will be initiated to increase the RDE 2 RE sample size to 21 patients and Simon's 2-stage design will be applied in the same manner as planned for RDE 1. Given this, the total number of RE patients for RDE 2 may be 18, 21, or 35.
- *3L NSCLC TAK-500 SA RDE 1 versus RDE 2 [1:1 randomization]:*
  - Based on an exact binomial 1-stage design, approximately 24 patients will be enrolled each in the RDE 1 cohort and the RDE 2 cohort allowing for 21 RE patients per cohort. For each cohort, H_0: ORR ≤ 5%, H_A: ORR ≥ 20%, and power = 82%. The total RE sample size across the 2 cohorts will be 42 patients.

- *2L pancreatic adenocarcinoma TAK-500 + pembrolizumab RDE 1 versus 2L pancreatic adenocarcinoma TAK-500 SA RDE 1 [1:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 45 patients will be enrolled each in the combination cohort and the SA cohort, allowing for 40 RE patients per cohort. For each cohort, H_0: ORR $\leq$ 16%, H_A: ORR $\geq$ 30%, and power = 80%. For each cohort, a futility analysis will occur at 25 RE patients, where $\geq$ 4 responders are required to continue enrollment.
- *3L RCC TAK-500 + pembrolizumab RDE 1:*
  - Based on an exact binomial 1-stage design, approximately 34 patients will be enrolled allowing for 30 RE patients. H_0: ORR $\leq$ 8%, H_A: ORR $\geq$ 25%, and power = 90%.

For non-commercial use only

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

No formal statistical hypothesis testing will be performed. 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.

Efficacy and safety data will be summarized by escalation or expansion cohort; unscheduled visits will only appear in the listings. 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 first dose of study medicine or before first dose of planned pre-medication, if available. Cycle 1 Day 1 values are considered pre-dose.

Means and medians will be presented to 1 more decimal place than the recorded data. 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. Minimums and maximums will be presented using the same number of decimal places as the recorded data.

For non-commercial use only

Summary tables will include data for each study cohort (specific dose level and pre-medication regimen combination) and the overall study population for the SA and combination dose escalation and dose expansion arms, as appropriate; For PK analyses, cohorts with the same dose level and arm (SA or combination) may be combined across pre-medication regimens. In the event that alternative dosing schedules are investigated, summary tables will also be broken out by schedule. Patients in the SA arm who crossover to the combination arm after progressive disease will have data after the point of crossover analyzed separately, i.e., the main analyses may be repeated as appropriate to show long-term safety and antitumor activity.

Screen failure patients will be grouped and listed.

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

7.1.1 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of study drug(s). 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.

7.1.2 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. Missing date conventions are stated in the PDS.

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 any study drug (i.e., TAK-500 or pembrolizumab) will be used for all safety analyses and for antitumor activity 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 who receive all required doses of TAK-500 (with pembrolizumab if in a combination cohort) and remain on study for 21 days from first dosing of TAK-500 (through C1D21) without experiencing a DLT or who have a DLT during the first 21 days after study drug administration. The DLT-evaluable population in the TAK-500 SA and the TAK-500 + pembrolizumab combination dose escalation cohorts will be used to determine the MTD. The MTD for TAK-500 SA may be different than the MTD for TAK-500 + pembrolizumab (specific pre-medication regimens to be evaluated separately).
- **Response-evaluable analysis set**: The response-evaluable analysis set, a subset of the safety analysis set, will include patients with measurable disease at baseline and at least 1 posttreatment tumor evaluation.
- **Peripheral pharmacodynamic analysis set**: The peripheral pharmacodynamic analysis set will include patients from the safety population who have been on study for at least 1 week and have baseline and at least 1 postbaseline peripheral sample assessment.
- **Tumor biopsy analysis set**: The tumor biopsy analysis set will include patients from the safety population who have baseline and at least 1 postbaseline tumor biopsy sample assessment.
- **Immunogenicity analysis set**: The immunogenicity analysis set consists of patients who receive at least 1 dose of TAK-500 and have an ADA status assessment at baseline, and at least 1 postbaseline sample.
- [redacted]

The number of patients in the safety analysis set, pharmacokinetics analysis set, DLT-evaluable analysis set, response-evaluable analysis sets, peripheral pharmacodynamic analysis set, tumor biopsy analysis set, immunogenicity analysis set, [redacted] will be summarized.

For non-commercial use only

Patients in the SA arm who cross over to the combination arm may be analyzed separately using all post-crossover data, repeating the main analyses as appropriate, to show long-term safety and antitumor activity. These crossover patients will still be included in the main analyses, in which their post-crossover data will be excluded.

Patients treated with a specific pre-medication regimen will be analyzed separately from cohorts treated without pre-medication or with other pre-medication regimens.

7.3 Disposition of Patients

Disposition of patients includes the number and percentage of patients in each escalation or expansion cohort and will be presented by these cohorts and overall for patients in the safety population. 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

Patient demographic and baseline characteristics will be summarized descriptively by escalation or expansion cohort and overall. For continuous variables, descriptive statistics (number of observations, 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.

Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate. Age will be calculated from date of birth to date of informed consent. No inferential statistics will be generated.

Baseline disease characteristics will include tumor types and associated disease characteristics as collected in the case report form.

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, prior radiation, prior surgery, and best response to the last prior anticancer therapy.

Demographic data, baseline disease characteristics, and prior therapies will also be presented in by-patient listings.

Throughout the study, baseline assessments are defined as the last observed value before the first dose of study medicine or before the first dose of planned pre-medication, if available. In the post-crossover analysis, baseline values for patients who crossover from the SA arm to the combination arm are defined as the last valid value before exposure to the combination drug.

7.5 Medical History and Concurrent Medical Conditions

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).

For non-commercial use only

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 WHO drug generic term for the safety population, from informed consent form (ICF) signature dose of study treatment, and 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.

Both medical history and concomitant medications will be summarized in tables.

7.6 Study Drug Exposure and Compliance

Extent of Exposure:
The exposure to TAK-500 and pembrolizumab will be characterized by total amount of dose taken, total number of doses taken, relative dose intensity (%) by cycle and overall, number of treated cycles, and numbers and percentages of patients who had ≥1, ≥2, …, ≥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) will be summarized for patients in the safety population.

The extent of exposure will be summarized by escalation or expansion cohort and overall.

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

Action on Drug:
Action on study drug (e.g., dose reduced due to AE) will be summarized by cycle and total for each escalation or expansion cohort and overall. Aggregate summaries such as by Cycles 1-6, 7-12, and 13-17 may also be provided if deemed appropriate.

For non-commercial use only

7.7 Efficacy Analysis

For the dose escalation phase, antitumor activity is not the primary endpoint; secondary antitumor activity endpoints include ORR, DCR, DOR, and TTR. In the dose expansion phase, ORR is the primary endpoint; secondary antitumor activity endpoints include DCR, DOR, TTR, PFS, and OS. No formal statistical tests will be performed for these efficacy endpoints. Instead, they will be summarized descriptively for each escalation or expansion cohort and overall. Response assessments are evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 by investigator at each timepoint and the best overall response for each patient will be derived programmatically from the reported responses. The sum of viable target lesion diameters and percent change from baseline will be reported using the response-evaluable analysis set. For confirming PR and CR, the confirmatory assessment should occur at least six weeks (-3 days allowable) after the initial assessment, as described in the protocol SOE. Further information for confirmed CR and PR is in the PDS.

7.7.1 Primary Efficacy Endpoint

In the dose expansion phase, ORR is the primary efficacy endpoint and is defined as the proportion of patients who achieve cCR or cPR (determined by the investigator) during the study among response-evaluable patients.

7.7.2 Secondary Efficacy Endpoints

For the dose escalation phase, secondary efficacy endpoints are ORR, DCR, DOR, and TTR. For the dose expansion phase, the secondary efficacy endpoints include DCR, DOR, TTR, PFS, and OS.

ORR is defined as the proportion of patients who achieve cCR or cPR (determined by the investigator) during the study. The primary analysis of ORR will be based on the response-evaluable analysis set. As a supplementary analysis, ORR will also be analyzed using the safety analysis set.

DCR is defined as the proportion of patients who achieve SD or better (determined by the investigator) for ≥ 6 weeks during the study in the response-evaluable analysis set. As it is permissible to perform tumor scans up to three days before the target six-week assessment timepoint, these early scans are also eligible for consideration in the establishment of disease control. Additionally, time will be counted from initial study treatment administration, therefore disease control could be claimed for a patient at their first six-week tumor assessment.

For non-commercial use only

DOR is defined as the time from the date of first documentation of a cPR or better to the date of first documentation of PD or death for responders (cPR or better) in the response-evaluable analysis set. 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 the PDS.

TTR is defined as the time from the date of first dose administration to the date of first documented cPR or better (determined by the investigator) in the response-evaluable analysis set among responders (cPR or better).

PFS is defined as the time from date of study treatment to the first documented disease progression based on RECIST v.1.1, or death due to any cause, whichever occurs first, in the safety analysis set. Censoring rules are presented in the PDS.

OS is defined as the time from the date of first dose administration to the date of death in the safety analysis set. For right-censored patients, the time of censoring is the last known date alive or the database cut-off date, whichever comes first.

ORR and DCR will be summarized using descriptive statistics with 95% CIs. DOR and TTR will be reported using basic summary statistics or analyzed using a Kaplan-Meier approach if feasible. PFS and OS will be analyzed using the Kaplan-Meier method in dose expansion cohorts only. Efficacy results will be reported by escalation or expansion cohort and overall.

Responses achieved in the crossover patients and long-term durability of response may be reported; if so, they will be presented separately from the main study data.

7.8 Examination of Subgroups

Efficacy endpoints, in particular ORR, may be presented by subgroups using the expansion phase cohorts. The below table (7.a) lists the clinical variables and categories defining subgroup analyses of potential interest, but additional subgroups may also be considered. If the percentage of patients within a particular subgroup is small, then the subgroup categories may be refined prior to presenting results.

Table 7.a: Potential Subgroup Analyses

Clinical Variable	Categories
PD-L1 expression	PD-L1 negative, low, med, high
Prior anti-PD-(L)1 therapy	Prior exposure to anti-PD-(L)1 therapy (yes/no), specific therapy to which exposed
Prior chemotherapy	Prior chemotherapy exposure (yes/no), specific chemotherapy agents to which exposed
Prior TKI	Prior TKI exposure (0, 1, or 2 lines of prior therapy), specific agents to which exposed
STING variants	Response based on germ-line STING variants
RAS mutation status	Mutation present (yes/no), specific mutation
STK11 Mutational status	Mutation present (yes/no), specific mutation
KEAP 1 mutational status	Mutation present (yes/no), specific mutation
HRD mutation status	BRCA1/2, ATM, PALB2, RAD51, etc.
Baseline STING RNA signature	Data driven category selection
Intratumoral CCR2 expression	Data driven category selection
Intratumoral MDSC/TAM infiltration	Data driven category selection
Presence of liver metastases	Liver mets present (yes/no)
Microsatellite status	MSI-H, MSI-L, MSS
MMR Status	dMMR/pMMR
TMB Status	TMB high/med/low, specific mut/Mb
Response to prior anti-PD-(L)1 therapy	If in palliative setting: exposure >6 months/<6 months If in adjuvant setting: recurrence >6 months after completion of therapy/<6 months after completion of therapy

For non-commercial use only

Molecular subtypes in PDAC, NSCLC or RCC shown to correlate with response to IO therapy	Data driven category selection

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic (PK) Analysis

7.9.1.1 PK Noncompartmental Analysis

PK parameters for TAK-500 will be estimated using noncompartmental methods with WinNonlin software. 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:

- C_{max}: the maximum observed concentration
- t_{max}: time of first occurrence of C_{max}
- AUC_t: area under the concentration-time curve from time 0 to time t
- AUC_∞: area under the concentration-time curve from time 0 to infinity
- $t_{1/2z}$: terminal disposition phase half-life
- CL: total clearance after intravenous administration
- V_{ss}: Volume of distribution at steady state after intravenous administration

For non-commercial use only

PK parameters will be summarized using descriptive statistics. Individual TAK-500 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by escalation or expansion cohort. Individual and mean concentration-time profiles will be plotted by escalation or expansion cohort. A summary of total antibody and/or deconjugated TAK-676 concentration-time data and PK parameters will be included (if measurable).

7.9.1.2 PK Sample Intended for Population PK Analysis

The PK data collected in this study are intended to contribute to future population PK analyses of TAK-500. These population PK analyses may additionally include data collected in other TAK-500 clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

7.9.2 Immunogenicity Analysis

Immunogenicity parameters (ADA-negative, transiently and persistently ADA-positive, low or high ADA titer) will be analyzed using descriptive statistics in the safety analysis set and immunogenicity

analysis set. The relationship of immunogenicity responses to PK, antitumor activity, and safety may be explored.

7.9.3 Pharmacodynamic Analysis

The [redacted] will be evaluated in peripheral blood (peripheral pharmacodynamic analysis set) and/or tumor samples (tumor biopsy analysis set) collected at baseline and after administration of TAK-500. The change [redacted] will be calculated and used to establish evidence of pharmacodynamic modulation. The relationship between [redacted] may also be explored. Results will be included selectively in the clinical study report; in particular, RNA signature, key cytokine, key flow, and CD8 infiltration in the tumor will be included.

For non-commercial use only

7.10 Other Outcomes

7.10.1 PK/Pharmacodynamics Analysis

The relationship between TAK-500, total antibody, and/or deconjugated TAK-676 exposure and pharmacodynamic response [redacted] will be explored on an ongoing basis as PK and pharmacodynamic data become available to understand the PK-pharmacodynamic relationship of TAK-500 and to help in estimation of the PAD range. Data permitting, mathematical models may be used to describe this relationship and such models may be used to predict the dose/schedule of TAK-500 that provides the desired exposure and pharmacological response for future evaluation. These data may be presented graphically as well as summarized in the clinical study report. The analysis will be performed in the peripheral pharmacodynamic analysis set.

7.10.2 PK/ QTc Analysis

The PK-time matched triplicate ECG data collected in each patient will be pooled to understand the PK-QTc relationship of TAK-500. The relationship between TAK-500 serum concentration and effects on heart rate and QTcF will be analyzed using mixed effects modeling. These population PK-QTc analyses may include data collected in other TAK-500 clinical studies. As such, the analysis plan for the population PK-QTc analysis will be separately defined, and the results of these analyses will be reported separately and not presented in the clinical study report for this study.

7.11 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.

7.11.1 Dose Limiting Toxicities (DLTs)

The incidence of DLTs will be tabulated for each escalation or expansion cohort in the DLT-evaluable analysis set. In addition, to assess the relationship between toxicities and TAK-500 doses, the preferred term of individual toxicities will be summarized by frequency and intensity for each escalation or expansion cohort.

A by-patient listing of DLTs will be presented by escalation or expansion cohort. Patients will be grouped by the escalation or expansion cohort to which they were originally assigned.

7.11.2 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 and through 30 days after the last dose of any study drug.

Treatment-related immune-mediated AEs as determined by the investigator that occur 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) will be tabulated.

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

For non-commercial use only

- Treatment-emergent AEs
- Treatment-related immune-mediated AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Treatment-related grade ≥ 4 AEs in any nonhematologic system organ class (excepting grade ≥ 4 asymptomatic laboratory abnormalities); see PDS for definition
- 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

- Treatment-emergent AEs leading to death

Whenever AEs are grouped by "treatment-relatedness", they will be summarized in three mutually exclusive groups: related to TAK-500, related to pembrolizumab, and related to both TAK-500 and pembrolizumab.

Adverse events will be summarized with the number and percentage of patients experiencing each adverse event. 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. The cumulative occurrence frequencies of each AE may also be summarized next to the patient numbers and percentages.

Details for each category are described below.

7.11.2.1 Treatment-emergent Adverse Events

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

The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥ 10% of all patients) will be tabulated by preferred term.

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.

7.11.2.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment emergent SAE 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).

7.11.2.3 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 the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug unless the death is due to a related immune mediated AE through 90 days after the last dose of any study drug. 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.

For non-commercial use only

7.11.2.4 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 escalation or expansion cohort and overall.

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

7.11.2.5 Cytokine Release Syndrome (CRS)

The number and percentage of patients experiencing a CRS event, a CRS event as an SAE, a CRS event that leads to dose reduction, or a CRS event that leads to treatment discontinuation will be reported. Additionally, the number of CRS events and number and percentage of CRS toxicity grades, CRS signs/symptoms, and outcomes will be reported. The duration of CRS event will also be reported. All above will be summarized by escalation or expansion cohort and cycle of CRS onset (including overall). The above information will be presented in a table separate from the other TEAE tables.

A by-patient listing of CRS events and a by-patient listing of concomitant medications associated with CRS events will be presented. Additionally, a swimmer plot depicting CRS event timing and duration of patient study-time will be generated; this will be presented by escalation or expansion cohort.

The number and percentage of patients experiencing a CRS event who received Tocilizumab (overall, by CRS grade, and by number of Tocilizumab doses) and the number and percentage of CRS events treated with Tocilizumab (overall and by CRS grade and by cycle) will be reported in a table. Results will be summarized by escalation or expansion cohort.

For non-commercial use only

7.11.3 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.

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

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline vs. worst postbaseline values, may be used to understand the TAK-500 safety profile.

Parameters to be tabulated are included in Table 7.b:

Table 7.b: Hematology, Thyroid Function, Tumor, Clinical Chemistry, and Coagulation Tests

Hematology	**Serum Chemistry**	
Hematocrit	Protein (total)	Magnesium
Hemoglobin	Albumin	Phosphate
Leukocytes with differential	ALP	Potassium
Neutrophils (ANC)	ALT	Sodium
Platelets (count)	AST	Chloride
Erythrocytes (RBC)	Bilirubin (total)	Urate
MCH	Glucose (fasting not required)	
MCV	Lactate dehydrogenase	
MCHC	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	aPTT	
Thyroxine, free	PT or prothrombin international normalized ratio	
Tumor Markers	**Other**	
AFP (HCC)	Ferritin	
CA 27.29 (TNBC)	Creatine kinase	
	IL-6	
CA 19-9 (pancreatic adenocarcinoma)	Troponin I	
	HbA1c	

ANC: absolute neutrophil count; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; HbA1c: glycosylated hemoglobin; HCC: hepatocellular carcinoma; IL-6: interleukin 6; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; RBC: red blood cell; TNBC: triple-negative breast cancer.

For non-commercial use only

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 parameters.

7.11.4 Vital Signs

The actual values of vital sign parameters (blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), height, and weight will be summarized over time [redacted] 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.

7.11.5 Safety ECGs

Both standard 12-lead ECGs and triplicate ECGs are used in the study. While cardiac safety monitoring should be primarily performed with standard 12-lead ECGs, triplicate ECGs may also be used in certain circumstances. Refer to section 9.4.11 of the protocol for details of use of the two types of ECGs. The SAP will only focus on the ECG data collected for safety monitoring purposes.

A summary of ECG abnormalities will be presented by visit. 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.

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 ≥ 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 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.

For non-commercial use only

7.11.6 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 escalation or expansion cohort and overall.

7.11.7 [redacted]

[redacted]

7.11.8 [redacted]

[redacted]

7.11.8.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.11.9 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.

For non-commercial use only

7.12 Protocol Deviations

All significant protocol deviations will be presented as a table and listing, which will include at least the following categories:

- Patients entered the study even though they did not satisfy the entry criteria
- Patients developed withdrawal criteria but were not withdrawn
- Patients received the wrong treatment or incorrect dose
- Patients received an excluded concomitant medication

7.13 Criteria for Early Termination

In the dose escalation, although no formal interim analysis is planned, investigators and sponsor representatives will review all available data to determine dose escalation and number of patients per cohort.

In the dose expansion phase, futility analyses based on Simon's 2-stage design are planned for two indications (refer to Section 6.0 for details):

- *2L NSCLC TAK-500 + pembrolizumab RDE 1 versus RDE 2 [2:1 randomization]:*

  - Based on Simon's 2-stage design, a maximum of 35 clinically response-evaluable patients will be required for analysis of ORR in the RDE 1 cohort. The futility analysis will occur at the time that 21 clinically response-evaluable patients are available for assessing ORR, where ≥ 5 responders are required to continue enrollment.
  - If the futility analysis in RDE 1 determines that enrollment within RDE 1 should stop, the RDE 2 cohort will enroll (maximum of 35 clinically response-evaluable patients) until a futility analysis is performed at the time that 21 clinically response-evaluable patients are available for assessing ORR, where ≥ 5 responders are required to continue enrollment.

- *2L pancreatic adenocarcinoma TAK-500 + pembrolizumab RDE 1 versus 2L pancreatic adenocarcinoma TAK-500 SA RDE 1 [1:1 randomization]:*
  - Based on Simon's 2-stage design, a maximum of 40 clinically response-evaluable patients will be required per cohort for analysis of ORR. For each cohort, a futility analysis will occur at the time that 25 clinically response-evaluable patients are available for assessing ORR, where ≥ 4 responders are required to continue enrollment.

7.14 Stopping Rules

During the initial phase of escalation, if the study enters a 3+3 design due to toxicity in either of the first two dose levels, the escalation will stop when there are at least 2 DLTs observed in a dose level. After the study enters the BOIN design, the escalation will stop if the posterior probability of exceeding the target toxicity rate is greater than 0.95. Otherwise, the escalation will continue until either (1) the maximum sample size is reached, or (2) 9 patients have been treated with the current dose level and the recommendation is to stay at the current dose level.

During the escalation and expansion phases, a threshold of fatal AEs related to TAK-500 SA or TAK-500 + pembrolizumab combination therapy will initially be set at 6% per study arm. Any rate of fatal events related to TAK-500 SA or TAK-500 + pembrolizumab combination therapy that is over 6% with at least an 80% posterior probability (as calculated using the number of enrolled patients) will result in stopping the study. The study will also be stopped if the rate of TAK-500 SA-related or TAK-500 + pembrolizumab combination therapy-related Grade ≥ 4 events in any nonhematologic System Organ Class exceeds 25% per arm (with the exception of Grade ≥ 4 asymptomatic laboratory abnormalities) with at least an 80% posterior probability (as calculated using the number of enrolled patients). A study stop for a safety issue will result in an immediate halt in enrollment and may also necessitate cessation of treatment of ongoing patients, depending on the nature and the severity of the safety risk. A final decision to terminate the study will be made only after a full review of the safety data by the sponsor and the safety management team.

Beyond these conditions, the sponsor may stop or halt enrollment or treatment of ongoing patients, depending on the nature and severity of a safety-related event. 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.

For non-commercial use only

7.15 Changes in the Statistical Analysis Plan

To be updated as needed (See Appendix 9.1).

7.16 Changes to Protocol Planned Analyses

[redacted]

For disease control rate (DCR), the criterion for control was changed from "> 6 weeks" to "≥ 6 weeks" and made more flexible to allow for tumor assessments occurring up to 3 days before the 6-week target.

For non-commercial use only

8.0 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.

For non-commercial use only

9.0 APPENDICES

9.1 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:

SAP Section	Impacted Text	Change	Rationale for Change
4.1	Description of study design and corresponding escalation figure (4.a)	Updated study design and figure to correspond with PA 3	PA 3
4.3-4.5	List of primary objectives, secondary objectives, and exploratory objectives	Updated objectives to correspond with PA 3	PA 3
5.1-5.3	List of primary, secondary, and exploratory endpoints	Updated endpoints to correspond with PA 3 and further detail included for DCR	PA 3
6.0	Sample size, sample size justification, general analysis methods, and futility analyses	Updated sample size and analysis plan to correspond with PA 3	PA 3
7.1.3-7.1.6	Missing data conventions	Removed and added to the PDS	Introduction of required PDS document
7.2	DLT-evaluable analysis set [redacted]	Clarification of DLT-evaluable analysis set definition; [redacted]	Clarification and new addition from PA 3, respectively
7.2	Crossover and pre-medication cohorts	Updated language regarding handling of crossover and varying pre-medication cohort analyses	Clarification and new addition from PA 3

For non-commercial use only

7.6	TAK-500 RDI	Details regarding RDI removed and added to PDS	Introduction of required PDS document
7.7	Overall efficacy analysis description, primary efficacy endpoint, and secondary efficacy endpoints	Updates to efficacy analysis based on PA 3	PA 3
7.8	Addition of an exploratory subgroup analysis section	New section added	New section requested by study team
7.11.2.5	CRS safety analysis	Section added to Safety Analysis describing the presentation of CRS events	PA 3 and presence of a large number of CRS events in study
7.11.3	Clinical laboratory measurements (Table 7.b)	IL-6 added to table 7.b as a lab measurement of interest	PA 3
7.11.3	Cockcroft-Gault formula	Removed and added to PDS	Introduction of required PDS document
7.11.5	Fridericia's rate-corrected QT intervals formula	Removed and added to PDS	Introduction of required PDS document
7.11.7	Continuous Vital Sign Data Analysis	Brief section added describing the use of continuous vital sign monitoring (Biobeat)	PA 3
7.11.8	[redacted]	[redacted]	PA 3

For non-commercial use only

		approach used in TAK-676-1002	
7.13	Criteria for Early Termination	Early termination criteria for expansion described in greater detail	PA 3
7.14	Stopping Rules	Bayesian rules for study stopping due to safety added from protocol	PA 2/3
7.16	Changes to Protocol Planned Analyses	This section was added	Inconsistencies with current protocol
Appendix 9.2	Summary of the Best Overall Response Status Calculation when Confirmation of CR and PR is Required	Removed and added to PDS	Introduction of required PDS document
Appendix 9.3	Censoring Rules for DOR and PFS	Removed and added to PDS	Introduction of required PDS document

For non-commercial use only

Signature Page for TAK-500-1001 Statistical Analysis Plan V2 20 Feb 2024
Title:

Approval	[redacted] Statistics 23-Feb-2024 20:21:35 GMT+0000

Document Number: TDN-000242749 v1.0

For non-commercial use only