



Statistical Analysis Plan

NCT Number: NCT04844073

Title: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of TAK-186 (Also Known as MVC-101), An EGFR x CD3 COnditional Bispecific Redirected Activation (COBRA) Protein in Patients With Unresectable Locally Advanced or Metastatic Cancer

Study Number: CP-MVC-101-01

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STATISTICAL ANALYSIS PLAN

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Phase: 1/2

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Amendment 1		To make SAP consistent with Amendment 7 of the protocol

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TABLE OF CONTENTS

1.0	OBJECTIVES, ENDPOINTS AND ESTIMANDS	9
1.1	Objectives	9
1.1.1	Primary Objective	9
1.1.2	Secondary Objective(s)	9
1.1.3	Exploratory Objectives	9
1.2	Endpoints	10
1.2.1	Primary Endpoint(s)	10
1.2.2	Secondary Endpoints	10
1.2.3	Exploratory Endpoints	10
2.0	STUDY DESIGN	11
2.1	Dose Escalation Phase	12
2.2	Cohort Expansion Phase	14
3.0	STATISTICAL HYPOTHESIS AND DECISION RULES	14
4.0	SAMPLE-SIZE DETERMINATION	15
5.0	ANALYSIS SETS	15
6.0	STATISTICAL ANALYSIS	16
6.1	General Considerations	16
6.1.1	Handling of Treatment Misallocations	16
6.1.2	Analysis Approach for Continuous Variables	16
6.1.3	Analysis Approach for Categorical Variables	16
6.1.4	Analysis Approach for Time-to-Event Variables	17
6.2	Disposition of Subjects	17
6.2.1	Patient Disposition	17
6.2.1	Protocol Deviations	17
6.2.1	Missed Visits due to COVID-19	17
6.3	Demographic and Other Baseline Characteristics	17
6.3.1	Demographics and Baseline Characteristics	18
6.3.2	Tobacco Usage	18
6.3.3	Medical History and Concurrent Medical Conditions	18
6.3.4	Disease Characteristics	18
6.4	Inclusion and Exclusion Criteria	19
6.5	Medication History and Concomitant Medications	19
6.5.1	Medications	19
6.5.2	Systemic Cancer Therapy	19

6.5.3	Cancer Related Surgery	19
6.5.4	Radiotherapy	20
6.6	Efficacy Analysis	20
6.6.1	Primary Endpoint(s) Analysis	20
6.6.2	Secondary Endpoint(s) Analysis	20
6.6.2.1	Derivation of Endpoint(s)	20
6.6.2.2	Main Analytical Approach	20
6.6.3	Other Secondary Endpoints Analysis (if applicable)	23
6.7	Safety Analysis	24
6.7.1	Non-CRS Adverse Events	24
6.7.2	CRS	26
6.7.3	DLT	27
6.7.4	Clinical Laboratory Evaluation	27
6.7.5	Vital Sign Measurements	28
6.7.6	ECOG	28
6.7.7	ECGs	28
6.7.8	Extent of Exposure and Compliance	29
6.8	Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses	30
6.8.1	Pharmacokinetic Analysis	30
6.8.2	Pharmacodynamic Analysis	31
6.8.3	Immunogenicity Analysis	31
6.8.4	Biomarker Analysis	31
6.9	Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis	31
6.9.1	PRO Analysis	31
6.9.2	Health Care Utilization Analysis	31
6.10	Interim Analyses	32
6.11	Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]	32
7.0	REFERENCES	33
8.0	CHANGES TO PROTOCOL PLANNED ANALYSES	34
9.0	CHANGES FROM THE PREVIOUS VERSION OF THE SAP	34
10.0	APPENDIX	35
10.1	Definition of Baseline	35
10.2	Definition of Best Overall Response	35

10.3	Handling of Missing or Partial Dates.....	36
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LIST OF IN-TEXT TABLES

Table a	Censoring Rules per RECIST v1.1	21
Table b	Censoring Rules per modified RECIST v1.1.....	23
Table c	Futility Boundary at the Interim Analysis for Each Cohort.....	32
Table d	Best Overall Response When Confirmation of CR, PR and PD Are Required.....	36

LIST OF IN-TEXT FIGURES

Figure a	Study Treatment Schema.....	12
Figure b	Dose Escalation Plan in Single-Patient Cohorts.....	13

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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
AUC _{inf}	Area under the concentration-time curve from time 0 to infinity
AUC _{last}	Area under the concentration-time curve from time 0 to last observation
AUC _{tau}	Area under the concentration-time curve for a dose administration interval
BLQ	lower limit of quantification
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CL	Total clearance
C _{max}	Maximum observed plasma concentration
CR	Complete Response
CRC	Colorectal Cancer
CRS	Cytokine Release Syndrome
CTMS	Clinical Trial Management System
ctDNA	Circulating tumor DNA
CV	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
HNSCC	Head and neck squamous cell cancer
HPV	Human papillomavirus
IV	Intravenous
■	■
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QW	Once Weekly
RDE	Recommended Doses for Expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
StD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Events
T _{max}	Time to reach maximum observed plasma concentration

ULN	Upper Limit Normal
WHO	World Health Organization

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1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of this study is:

- To characterize the safety, tolerability, and dose-limiting toxicities (DLTs) of TAK-186 when administered IV once weekly (QW) to patients with unresectable, locally advanced or metastatic cancer.

1.1.2 Secondary Objective(s)

The secondary objectives of the study are to:

- Determine the recommended phase 2 dose (RP2D) of TAK-186 when administered IV QW to patients with unresectable, locally advanced or metastatic cancer.
- Characterize the PK and immunogenicity of TAK-186.
- Evaluate the preliminary antitumor activity of TAK-186 in patients with unresectable, locally advanced or metastatic cancer.
- Compare TAK-186 antitumor activity efficacy endpoints using conventional Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (Eisenhauer, et al., 2009) (see Appendix C of Protocol Amendment 7) versus modified RECIST v1.1 (Seymour, et al., 2017) (see Appendix D of Protocol Amendment 7).

1.1.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Explore the relationships between PK, pharmacodynamics, patient safety, and TAK-186 antitumor activity.
- Evaluate the relationship between tumor EGFR expression at baseline (pretreatment) and TAK-186 antitumor activity.
- Evaluate the relationship between tumor PD-L1 (programmed death-ligand 1) expression and TAK-186 antitumor activity.
- Evaluate the impact of tumor T-cell infiltration following TAK-186 administration.
- Evaluate the dose-response impact on tumor T-cell infiltration following TAK-186 administration.
- Evaluate the impact of TAK-186 on circulating immune cells and cytokines following TAK-186 administration.
- Evaluate changes in target expression, immune cell infiltration, and activation markers in baseline (pretreatment) versus on-treatment tumor biopsy specimens (eg, changes in tumor infiltration lymphocytes) to support dose selection.
- Evaluate circulating tumor DNA (ctDNA) pre- versus on-treatment and correlation with patient response data.

- Explore the tolerability of TAK-186 through collection of patient-reported symptomatic AEs and the overall patient-reported burden of these symptomatic AEs.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

The primary study endpoints are:

- Non-CRS AEs, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
- CRS, according to American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading (Lee, et al., 2019).
- DLTs during the dose escalation phase.

1.2.2 Secondary Endpoints

The secondary endpoints are:

- RP2D selected on the basis of comprehensive safety, PK, and efficacy data.

PK and Immunogenicity:

- Single- and multiple-dose PK parameters.
- ADAs, ADA titers; neutralizing ADAs (ADA-positive samples).

Efficacy:

- ORR: the proportion of patients achieving complete response (CR) or partial response (PR) according to RECIST v1.1 (both confirmed and unconfirmed) and modified RECIST v1.1.
- Duration of response (DOR): the time in weeks from initial confirmed objective response (CR or PR) to the time of documented PD or death from any cause, whichever occurs first. Objective response will be determined using both RECIST v1.1 and modified RECIST v1.1 response criteria.
- Progression-free survival (PFS): the time from the date of the first dose of study drug to the date of any documented confirmed PD, using both RECIST v1.1 and modified RECIST v1.1, or the date of death from any cause.
- OS: the time from the first dose of study drug until the date of death due to any cause.

1.2.3 Exploratory Endpoints

The exploratory endpoints are:

- EGFR expression in tumors.
- PD-L1 expression in tumors.
- Determination of fold change of immune cell markers including but not limited to total T cells, CD8+ and CD4+ T cell infiltration in pretreatment versus on-treatment biopsy specimens.

- Baseline assessment of biomarkers in the TME such as but not limited to tumor mutational burden (TMB) and microsatellite instability (MSI-high) status as well as immune cell infiltration of different immune cell populations, including but not limited to, CD4 and CD8 T-cells, NK (natural killer) cells, macrophages.
- Changes from baseline in peripheral blood immune cell markers assessed by flow cytometry (including but not limited to activation [CD8+, CD25+] or proliferation [CD8+, Ki67] markers).
- Changes from baseline in peripheral cytokine concentrations.
- Evaluation of changes in ctDNA levels pretreatment versus on-treatment.
- Description of patient-reported symptomatic AEs experienced over the course of the study, as measured by selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library and Functional Assessment of Cancer Therapy (FACT) item bank.
- Description of patient-reported overall side-effect burden, as measured by the single item FACT-GP5.

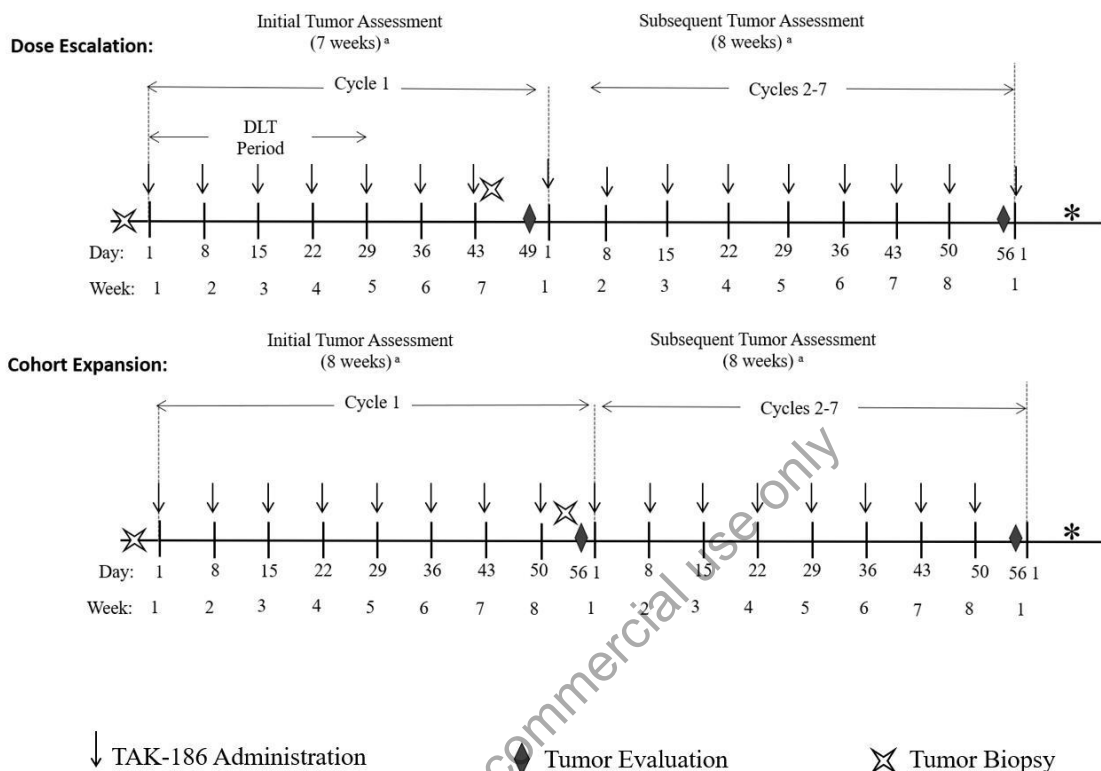
2.0 STUDY DESIGN

This is a phase 1/2, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of TAK-186 administered by IV infusion QW in patients with unresectable, locally advanced, or metastatic cancer. The study consists of a dose escalation phase to determine the MTD. The dose escalation phase will be followed by a cohort expansion phase to assess efficacy and safety of TAK-186 as monotherapy in unresectable, locally advanced or metastatic solid tumors expressing EGFR, including NSCLC, CRC, and HNSCC and may compare 2 different doses or regimens of TAK-186 during cohort expansion dose optimization in a 1:1 randomized fashion, if applicable.

TAK-186 will be administered by IV infusion weekly (QW). Treatment will be continued until disease progression, completion of 7 cycles in the event of no radiologic evidence of tumor regression, withdrawal of consent, or death, whichever occurs first. For patients who continue to receive clinical benefit at the end of the 7 cycles, tolerate TAK-186 well, and have no alternative treatment options, the investigator may request to continue study treatment, after discussion with the sponsor's medical monitor.

The study treatment schema is presented in [Figure a](#) Study Treatment Schema.

Figure a Study Treatment Schema



The DLT-evaluation period is defined as the time between the initial TAK-186 dose and Cycle 1 Day 28.

^a For both the dose escalation phase and cohort expansion phase, tumor assessment will be performed at the end of each cycle and results should be reviewed before initiating the next treatment cycle with TAK-186.

* All patients will complete the end-of-treatment (EOT) visit 30 (+10) days after the last dose of study drug and then be followed for survival every 12 weeks (see Appendix A of Protocol Amendment 7). The survival follow-up will be performed until the patient has died or is lost to follow-up or up to a maximum of 48 weeks after the last dose.

2.1 Dose Escalation Phase

Dose escalation is carried out in sequential cohorts of escalating doses ranging from [REDACTED]. The initial 2 cohorts are single-patient cohort escalation steps at [REDACTED] and then converted to a conventional 3+3 design. Intermediate doses may be explored during the dose escalation phase of the study, based on review of the cumulative safety data and upon agreement between the investigators and the sponsor.

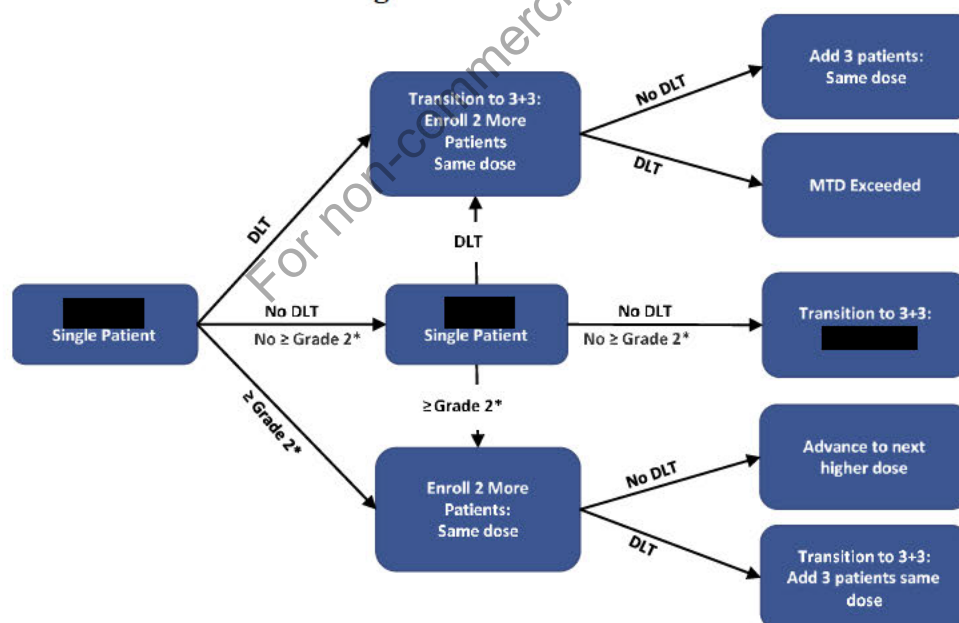
Detailed dose escalation rules are as follows:

Single-Patient Cohorts

- If no DLTs or drug-related grade 2 AEs (with exceptions, see Section 8.2 of the Protocol Amendment #7) occur in the [REDACTED] cohort, then a single patient will be enrolled into the [REDACTED] dose cohort.
- If no DLTs or drug-related grade 2 AEs (with exceptions, see Section 8.2 of the Protocol Amendment #7) occur in the [REDACTED] cohort, then dose escalation transitions to a 3+3 design at the [REDACTED] dose level.
- If a DLT occurs during the DLT evaluation period for either the [REDACTED] dose, escalation is transitioned to a 3+3 design enrolling 2 more patients at the dose level at which the DLT occurred (i.e., mimics the additional 3 patients enrolled in a 3+3 design).
- If a patient enrolled in a Single-Patient Cohort experiences a drug-related grade 2 AE (with exceptions, see Section 8.2 of the Protocol Amendment #7), the cohort will be expanded to enroll 2 more patients at the same dose to achieve a total of 3 patients. If 0 of these 3 patients experience a drug-related DLT during the DLT evaluation period, the dose will be escalated.

The dose escalation plan in Single-Patient Cohorts is depicted in Figure b below.

Figure b Dose Escalation Plan in Single-Patient Cohorts



AE: adverse event; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

* Only select Grade 2 AEs, per CTCAE v5.0 trigger moving to 3+3 design; See Section 8.3 Drug-Related Grade 2 AEs that will not trigger expansion to 3 patients in the single-patient cohorts.

3+3 dose escalation cohorts

- If none of the 3 patients in the initial cohort experience a DLT during the DLT evaluation period, the dose will be escalated, and 3 patients enrolled at the next higher dose level.
- If one of the first 3 patients treated at a given dose level experiences a DLT, then 3 additional patients will be enrolled at that dose level (total of 6 patients in this cohort). If none of these 3 additional patients experiences a DLT, the dose will be escalated, and 3 patients enrolled at the next higher dose level.
- If ≥ 2 patients out of the first 3 patients or ≥ 2 of 6 patients treated at a given dose level experience a DLT, then the MTD has been exceeded and the next lower dose is considered the MTD.

2.2 Cohort Expansion Phase

During the initial cohort expansion phase, approximately 30 patients with unresectable, locally advanced or metastatic NSCLC will be enrolled in a single arm cohort to receive TAK-186 with a dose determined from the dose escalation phase of the study. Dose selection for the cohort expansion phase will be based on the PK, pharmacodynamic, safety, and tolerability data from the dose escalation phase of the study.

Tumor assessment will be performed every 8 weeks (8 week/cycle) for patients enrolled in cohort expansion. An interim futility analysis is planned based on overall response rate (ORR) when the first 15 patients in the cohort become evaluable for efficacy by having at least 3 postbaseline scans or having discontinued therapy, whichever occurs earlier.

Based on the observed efficacy and safety data from the initial expansion cohort, more cohorts may be opened to assess different doses/regimens of TAK-186 in other EGFR expressing tumors, such as CRC and HNSCC, with approximately 30 patients in each tumor type. The RP2D will be determined at the end of the cohort expansion phase on the basis of the assessment of safety, PK, and efficacy data, including exposure-response analyses.

The primary analysis of this study will be carried out when all patients have discontinued therapy or, if continuing therapy, have data available through approximately 6 months of follow-up.

3.0 STATISTICAL HYPOTHESIS AND DECISION RULES

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Up to approximately 258 patients will be enrolled in this study.

For dose escalation, the number of patients is up to approximately 48 patients. Patients who are DLT non-evaluable during the DLT evaluation period will be replaced. More than 48 patients may be enrolled depending on results during the study and the number of TAK-186 doses evaluated. This number does not account for replacement of non-evaluable patients or the backfill patients.

Approximately 30 patients with NSCLC will be enrolled during the cohort expansion phase. Additional patients with EGFR expressing solid tumors, such as CRC and HNSCC, may be enrolled with approximately 30 patients per tumor type. Further, patients may be enrolled to allow comparison between 2 different doses or regimens of TAK-186 for selected tumor type(s) by 1:1 randomization to each dose/regimens (eg, 40 patients randomized 1:1 for NSCLC). Therefore, the total sample size of the cohort expansion phase of the study is estimated to be up to approximately 210 patients.

5.0 ANALYSIS SETS

The following populations will be used for analysis: the DLT-evaluable, safety (all-treated), PK, immunogenicity, and pharmacodynamics, and defined as follows:

DLT-evaluable population: all patients who receive at least 3 doses of TAK-186 in dose cohort [REDACTED], or at least 2 target doses of TAK-186 with [REDACTED] or experience a DLT within the DLT-evaluation period.

Safety population (All-Treated): all patients who receive at least 1 dose of TAK-186. This population will be used for safety and efficacy analyses. Patients who receive at least 1 dose of TAK-186 and have relevant blood sampling will be included in PK, immunogenicity, and pharmacodynamics analyses. Details are as follows:

PK population: all patients who receive at least 1 dose of TAK-186 and sufficient PK data to reliably estimate 1 or more PK parameters.

Immunogenicity population: all patients who receive at least 1 dose of TAK-186 and have a baseline immunogenicity sample and at least 1 postbaseline immunogenicity sample for assessment.

Pharmacodynamics population: all patients who receive at least 1 dose of TAK-186 and have sufficient dosing and pharmacodynamics data to reliably measure pharmacodynamics parameters.

PRO analysis population: all patients with a baseline and at least one postbaseline measurement of any PRO. The analyses of PROs will be based on the PRO analysis population set.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Safety and efficacy summaries will be provided by dose level and schedule in the Dose Escalation Phase, and by tumor type and RDE in the Cohort Expansion Phase. Refer to TLF shells for detailed header.

In descriptive summaries for safety, outliers (i.e., extreme relative to the majority of the data) will not be altered or removed from the summary. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients treated with that dose level and schedule (Dose Escalation Phase), or with that tumor type and RDE (Cohort Expansion Phase) within the analysis set of interest, unless otherwise specified.

The study day will be calculated as assessment date - first dose date + 1 if the assessment date is on or after the first dose date; it will be calculated as assessment date - first dose date if the assessment occurs prior to the first dose administration.

See [section 10.3](#) for data handling rules for missing or partial start/end dates.

All data are summarized based on the visit name collected on the electronic Case Report Form (eCRF) page.

All analyses will be conducted using SAS® Version 9.4 or higher (SAS® Institute, Inc., Cary, North Carolina, United States).

6.1.1 Handling of Treatment Misallocations

Not applicable.

6.1.2 Analysis Approach for Continuous Variables

Continuous data will be described using descriptive statistics (i.e., N, mean, standard deviation, median, minimum, and maximum) unless stated otherwise in the section specific to an endpoint.

6.1.3 Analysis Approach for Categorical Variables

Categorical data will be described using the patient count and percentage in each category unless stated otherwise in the section specific to an endpoint. The denominator for the percentage will be based on the number of patients in the corresponding analysis sets unless otherwise specified.

6.1.4 Analysis Approach for Time-to-Event Variables

Time-to-event data will be described using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated two-sided 90% confidence intervals as well as the survival probabilities at specified timepoints, unless otherwise specified.

6.2 Disposition of Subjects

The analyses will be performed using *Safety Population (All-treated)*.

6.2.1 Patient Disposition

The number and percentage of on study treatment patients, patients who have discontinued study treatment, the reasons for discontinuation of study treatment, patient who participate in survival follow-up, who are on study, who have discontinued from the study, and the reasons for discontinuation of study will be summarized.

Patient disposition data will also be presented in a data listing.

Patients who failed at screening and the reason for screen failure will also be presented in a data listing.

6.2.1 Protocol Deviations

Protocol deviations will be recorded within the PPD Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. The Study Deviations Rules Document contains all potential protocol deviations, classified by CTMS subtype. In addition, protocol deviation classification (e.g. significant vs. not significant) as determined by Takeda prior to database lock will be documented in CTMS.

All significant protocol deviations and activity subtype will be summarized.

All protocol deviations will also be presented in a data listing.

6.2.1 Missed Visits due to COVID-19

Information about missed visits or assessments due to COVID-19 will be recorded on a dedicated page in eCRF. The number and percentage of patients with at least one missed visits or assessments due to COVID-19, visit impact, reason for missing data, and impacted assessments will be summarized.

Missed visits or assessments due to COVID-19 will also be presented in a data listing.

6.3 Demographic and Other Baseline Characteristics

The analyses will be performed using *Safety Population (All-treated)*.

6.3.1 Demographics and Baseline Characteristics

The demographic and baseline characteristics consist of age (years), sex, race, and ethnicity. The baseline characteristics consist of childbearing potential (Yes/No) for female patients, Eastern Cooperative Oncology Group (ECOG) performance status, height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), respiration rate (breaths/min), temperature ($^{\circ}\text{C}$), and other parameters as appropriate. Demographic and baseline characteristics will be summarized. Categories for missing data will be presented as needed.

Demographic and baseline characteristics will also be presented in a data listing.

6.3.2 Tobacco Usage

Usage of cigarettes, cigars, pipes and vape will be summarized.

Tobacco usage data will also be presented in a data listing.

6.3.3 Medical History and Concurrent Medical Conditions

Medical history will be coded using the latest version of MedDRA and summarized. A patient with multiple occurrences of medical history with a SOC will be counted only once in that SOC. A patient with multiple occurrences of medical history with a PT will be counted only once within that PT. The number and percentages of patients with any medical history will be summarized overall and for each SOC and PT.

Medical history will also be presented in a data listing.

6.3.4 Disease Characteristics

Cancer history will be summarized, including primary diagnosis, time since histological or cytological diagnosis (years), disease status at time of first diagnosis (locally resectable, locally advanced unresectable, metastatic), time since diagnosis of metastatic disease (years), TNM tumor stage at time of first diagnosis, human papillomavirus (HPV) status (positive, negative, unknown) for patients with HNSCC, K-Ras mutation status (wild type, mutant, other) and category (microsatellite instability-high (MSI-H), microsatellite stable (MSS)) for patients with CRC, specific type of carcinoma (squamous cell carcinoma, adenocarcinoma, other) and EGFR mutation status (wild type, mutant, unknown) for patients with NSCLC.

Time since histological or cytological diagnosis and since diagnosis of metastatic disease will be derived as follows:

- Time since histological or cytological diagnosis (years): $(\text{Date of informed consent signature} - \text{Date of histological or cytological diagnosis}) / 365.25$
- Time since diagnosis of metastatic disease (years): $(\text{Date of informed consent signature} - \text{Date of diagnosis of metastatic disease}) / 365.25$

Cancer history will also be presented in a data listing.

6.4 Inclusion and Exclusion Criteria

All inclusion/exclusion criteria related information for screened patients will be presented in a data listing. The listing will include only the patients who did not meet at least one inclusion/exclusion criterion.

6.5 Medication History and Concomitant Medications

The analyses will be performed using *Safety Population (All-treated)*.

6.5.1 Medications

Prior and concomitant medications will be coded using the latest version of WHODrug.

Prior medications are defined as medications taken prior to the first dose of study treatment in Cycle 1.

Concomitant medications are defined as medications with a start date on or after the date of the first dose in Cycle 1 up to 30 days following the last dose of study treatment in the study OR with a start date prior to the date of first dose of study treatment and continued during treatment.

Prior medications will be presented in data listing. A separate listing will be provided for concomitant medications. If a medication starts prior to the first dose of study treatment and has a stop date after the first dose of study treatment or is ongoing, it will be flagged as both prior and concomitant medication.

6.5.2 Systemic Cancer Therapy

Prior and concomitant systemic cancer therapy will be coded using the latest version of WHODrug.

The number and percentage of patients who received at least one prior systemic cancer therapy, number of total prior anti-cancer therapies, number of prior systemic cancer therapy for locally advanced or metastatic disease, and best response to any line of therapy will be summarized descriptively. Prior systemic cancer therapy will also be summarized overall and by Anatomical Therapeutic Chemical (ATC) level 4 term (sorted in descending order) and PTs (sorted alphabetically within each ATC level 4 term).

All systemic cancer therapies will also be presented in the Prior and Concomitant systemic cancer therapy data listing and prior systemic cancer therapy will be flagged.

6.5.3 Cancer Related Surgery

Prior and concomitant cancer related therapy will be coded using the latest version of MedDRA.

The number and percentage of patients with at least one prior cancer related surgery will be summarized descriptively. Prior cancer related surgery will also be summarized overall and by SOC and PT. A separate summary will be provided for concomitant cancer related surgery.

All cancer related surgeries will also be presented in the Prior and Concomitant cancer related surgeries data listing and prior cancer related surgery will be flagged.

6.5.4 Radiotherapy

The number and percentage of patients with at least one prior radiotherapy and at least one concomitant radiotherapy will be summarized for each tumor location.

All radiotherapies, including details of tumor location, setting, dose and best response, will also be presented in the Prior and Concomitant Radiotherapy data listing and prior radiotherapy will be flagged. If a radiotherapy starts prior to the first dose of study treatment and has a stop date after the first dose of study treatment or is ongoing, it will be flagged as both prior and concomitant radiotherapy.

6.6 Efficacy Analysis

6.6.1 Primary Endpoint(s) Analysis

Not applicable. Efficacy is not the primary endpoint for this study.

6.6.2 Secondary Endpoint(s) Analysis

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

The analyses will be performed using *Safety Population (All-treated)*, based on RECIST v1.1 (Eisenhauer, et al., 2009).

6.6.2.1 Derivation of Endpoint(s)

ORR is defined as the percentage of patients who achieve confirmed CR or PR during the study.

DOR will be calculated for responders only, and is defined as the time from initial response (CR or PR) to the time of first documented PD or death, whichever occurs first.

PFS is defined as the time from the date of the first dose of study drug to the date of first documented PD or death, whichever occurs first.

OS is defined as the time from the first dose of study drug to the date of death due to any cause. Patients who are lost to follow-up or are not known to have died at the time of data-cut-off for analysis will be censored at last known alive date.

6.6.2.2 Main Analytical Approach

6.6.2.2.1 ORR

ORR will be summarized by frequencies and percentages, and point estimates with two-sided exact 90% CIs.

BOR will be summarized by frequencies and percentages. See Section 10.1.2 definitions of BOR based on RECIST v1.1.

DCR is the proportion of patients who achieve confirmed CR or confirmed PR or SD of any duration. DCR will be summarized by frequencies and percentages, and point estimates with two-sided 90% exact binomial CIs.

A swimmer plot will be provided: each patient's study treatment duration will be represented by a bar, with symbols to distinguish the status at the end of the bar (still on study treatment, discontinued study treatment due to PD or discontinued study treatment not due to PD) and all the tumor assessments overall responses up to the last available scan.

A waterfall plot for best percentage change from baseline in the sum of diameters will also be provided. The best percentage change from baseline is defined as the maximum decline in sum of diameters, observed up until date of subsequent anti-tumor therapy. Waterfall plots go from the worst value, such as greatest progression of disease, on the left side of the plot, to the best value, i.e., most reduction of tumor, on the right side of the plot (Socinski, et al., 2008).

The ORR, BOR, and DCR will also be presented in data listings.

6.6.2.2.2 DOR

This endpoint will be measured based on confirmed objective response.

The DOR in weeks will be calculated as follows:

- For patients who have PD or died, $DOR = (\text{Date of PD/death} - \text{Date of initial response} + 1) / 7$;
- For patients who are alive without documented PD, $DOR = (\text{Date of last tumor assessment that is SD or better} - \text{Date of initial response} + 1) / 7$.

Table a below specifies the scenarios, censoring rules and date of event/censored that will be carried out for the analysis using RECIST v1.1.

Table a Censoring Rules per RECIST v1.1

Scenarios	Event/Censored	Event/Censoring Date
No post-baseline tumor assessments and no death	Censored	Date of first dose of study drug
Available tumor assessments after initial response, but not known to have progressed or died according to data in the database	Censored	Date of last tumor assessment that is SD or better

Scenarios	Event/Censored	Event/Censoring Date
Death after two or more consecutive missed tumor assessments with no prior evidence of disease progression	Censored	Date of last tumor assessment prior to the first missed assessment
PD (one objective PD)	Event	Earliest date of PD
Death due to any reason without PD	Event	Date of death
Start of any new-anti cancer therapy with no prior evidence of disease progression	Censored	Date of last tumor assessment prior to the start of new anti-cancer therapy

The number and percentages of patients with an event, the reasons leading to event, the number of patients censored, and the reasons leading to censoring will be summarized.

The 25th percentile, median, and 75th percentile of DOR in weeks along with the corresponding two-sided 90% CIs will be estimated by the KM method. The CIs will be calculated using Brookmeyer and Crowley (1982) method (Brookmeyer & Crowley, 1982).

Corresponding plots of Kaplan-Meier curves of DOR will be presented.

The DOR will also be presented in data listings.

6.6.2.2.3 PFS

The PFS in weeks will be calculated as follows:

- For patients who have PD or died, $PFS = (\text{Date of PD/death} - \text{Date of first dose of study drug} + 1) / 7$;
- For patients who are alive without documentation of PD, $PFS = (\text{Date of last tumor assessment where response is not missing or unable to evaluate} - \text{Date of first dose of study drug} + 1) / 7$.

The number and percentages of patients with an event, the reasons leading to event, the number of patients censored, and the reasons leading to censoring will be summarized using the same censoring rules as DOR in [Table a](#).

The 25th percentile, median, and 75th percentile of PFS in weeks along with the corresponding two-sided 90% CIs will be estimated by the KM method. Additionally, PFS rates at 3 months, 6 months, and 12 months from the first dose of study drug will be computed along with two-sided 90% CIs by the KM method. The CIs will be calculated using Brookmeyer and Crowley (1982) method (Brookmeyer & Crowley, 1982). The time points will be displayed based on the data availability.

Corresponding plots of Kaplan-Meier curves of PFS will be presented.

The PFS will also be presented in data listings.

6.6.2.2.4 OS

The OS in weeks will be calculated as follows:

- For patients who have died: $OS = (\text{Date of death} - \text{Date of first dose of study drug} + 1) / 7$;
- For patients who are censored: $OS = (\text{Last date known to be alive} - \text{Date of first dose of study drug} + 1) / 7$;

The number and percentages of patients have died and the reasons leading to death, the number of patients censored, and the reasons leading to censoring will be summarized.

The 25th percentile, median, and 75th percentile of OS in weeks along with the corresponding two-sided 90% CIs will be estimated by the KM method. OS rates at 3 months, 6 months, 12 months, 18 months, and 24 months from the first dose of study drug will be computed along with two-sided 90% CIs. The CIs will be calculated using Brookmeyer and Crowley (1982) method (Brookmeyer & Crowley, 1982). The time points will be displayed based on the data availability.

Corresponding plots of Kaplan-Meier curves will be presented.

The OS will also be presented in data listings.

6.6.3 Other Secondary Endpoints Analysis (if applicable)

The analyses will be performed using *Safety Population (All-treated)*, based on modified RECIST v1.1 (Seymour, et al., 2017).

ORR, BOR, and DCR will be analyzed using the same methods as described in 6.6.2.2.1, based on modified RECIST v1.1. See Section 10.1.2 definitions of BOR based on modified RECIST v1.1.

DOR will be analyzed using the same methods as described in 6.6.2.2.2, based on modified RECIST v1.1.

Table b below specifies the scenarios, censoring rules and date of event/censored that will be carried out for the analysis using modified RECIST v1.1.

Table b Censoring Rules per modified RECIST v1.1

Scenarios	Event/Censored	Event/Censoring Date
No post-baseline tumor assessments and no death	Censored	Date of first dose of study drug
Available post-baseline tumor assessments, but not known to have	Censored	Date of last tumor assessment

progressed (i.e. confirmed PD) or died according to data in the database: 1. No unconfirmed PD in any post-baseline tumor assessments; - or 2. One unconfirmed PD followed by at least one subsequent tumor assessment with an overall response of SD, PR or CR (i.e. PD not confirmed).		
Death after two or more consecutive missed tumor assessments with no prior evidence of PD	Censored	Date of last tumor assessment before first missed assessment
Disease progression: 1. Two scans proving PD; - or 2. One scan proving PD and no subsequent adequate tumor assessment (i.e missing or NE as overall response).	Event	Earliest date of PD
Death due to any reason without PD	Event	Date of death
Start of any new-anti cancer therapy with no prior evidence of PD	Censored	Date of last tumor assessment prior to the start of new anti-cancer therapy

PFS will be analyzed using the same methods as described in 6.6.2.2.3 and censoring rules as in [Table b](#), based on modified RECIST v1.1.

6.7 Safety Analysis

6.7.1 Non-CRS Adverse Events

The analyses will be performed using *Safety Population (All-treated)*.

All AEs, except immune-related AEs, with start date from first dose of study drug until 30 days after the last dose of study drug, and immune-related AEs with start date from first dose of study drug until 90 days after the last dose of study drug will be considered TEAEs. Events meeting this definition will be those occurring during or after administration of the first dose of study drug. Events that existed before the first administration of study drug and then increased in

severity during or after the first administration of study drug will also be considered treatment-emergent.

Only TEAEs will be summarized in tables. Events before treatment (e.g., due to study-related procedure) will be listed.

TEAEs with a missing severity will be summarized in tables as Grade 3 but will be presented in the data listings with a missing severity. If a patient reported multiple occurrences of the same TEAE, only the most severe will be presented.

TEAEs with a missing relationship will be summarized in tables as 'Related'; but will be presented in the data listing with a missing relationship.

An overall summary table will display the number and percentage of patients who experience at least one event of any TEAE.

In addition, the following summary tables will display the number and percentage of patients by MedDRA System Organ Class (SOC) and preferred term (PT) (and CTCAE severity, when specified). Patients with multiple occurrences of events of the same preferred term and SOC will be counted once for each preferred term or SOC (at the highest severity and closest relationship to study drug, as applicable). These tables will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC:

- DLTs;
- All TEAEs;
- All TEAEs by maximum CTCAE severity grade;
- All TEAEs CTCAE severity Grade 3 or 4;
- Drug-related TEAEs;
- Drug-related TEAEs by maximum CTCAE severity grade;
- Drug-related TEAEs CTCAE severity Grade 3 or 4;
- Serious TEAEs;
- Serious TEAEs by maximum CTCAE severity grade;
- Serious TEAEs CTCAE severity Grade 3 or 4;
- Drug-related Serious TEAEs;
- Drug-related Serious TEAEs by maximum CTCAE severity grade;
- Drug-related Serious TEAEs CTCAE severity Grade 3 or 4;
- All deaths
- TEAEs leading to dose reduction;

- TEAEs leading to drug infusion interruption;
- TEAEs leading to dose delay;
- TEAEs leading to dose withdrawn;

The following summary tables will display the number and percentage of patients by PT only and will be ordered in descending order of PT:

- All TEAEs;
- Drug-related TEAEs;
- Serious TEAEs;
- Drug-related Serious TEAEs;
- Most frequent TEAEs (at least 10% of all patients).

The following data will also be presented in data listings:

- Serious TEAEs;
- AEs leading to dose reduction (TEAEs will be flagged);
- AEs leading to drug infusion interruption (TEAEs will be flagged);
- AEs leading to dose delay (TEAEs will be flagged);
- AEs leading to dose withdrawn (TEAEs will be flagged);
- AEs leading to death (TEAEs will be flagged);
- All deaths.
- All AEs (TEAEs will be flagged).

6.7.2 CRS

The analyses will be performed using *Safety Population (All-treated)*.

An overall summary table of CRS events will display the number and percentage of patients who experience each of the following:

- Any Treatment-Emergent CRS adverse events;
- DLT of CRS;
- CRS leading to dose reduction;
- CRS leading to drug infusion interruption;
- CRS leading to dose delay;

- CRS leading to dose withdrawn;
- The Maximum ASTCT grade of CRS;
- Outcome of the last CRS
- CRS signs and symptoms by SOC and PT;
- Grade 3 or above CRS signs and symptoms by SOC and PT;
- Time to onset of CRS event with respect to each [REDACTED] and full dose in hours, defined as start time of the earliest signs and symptoms of CRS onset – stop time of each infusion immediately before each CRS event;
- Time to resolution of CRS event in hours, defined as stop time of the latest signs and symptoms of CRS resolution – start time of the earliest signs and symptoms of CRS onset.

In addition, CRS by Grade vs. time profile and the Tocilizumab usage in patients in safety population with any Treatment-Emergent CRS adverse events will be summarized.

The summary statistics of the time to onset of CRS event with respect to each [REDACTED] and full dose in hours will be displayed with mean, median, minimum, and maximum by dose level/schedule in the Dose Escalation Phase only.

The Treatment-Emergent CRS adverse events, and use of anti-cytokine agents for patients in safety population with any Treatment-Emergent CRS adverse events (including drug name, dose, the administration time, the administration time relative to respective study drug dosing, and the grade of CRS incidence) will also be presented in data listings.

A Sanky plot of CRS events will be generated by dose day for each dosing regimen. The following categories will be displayed with different textures: no CRS, grade 1 CRS without tocilizumab, grade 1 CRS with tocilizumab, grade 2 CRS without tocilizumab, grade 2 CRS with tocilizumab, grade 3 CRS and above without tocilizumab, grade 3 and above CRS with tocilizumab, and no dose administrated.

6.7.3 DLT

The analyses will be performed using *DLT-evaluable Population*.

The frequencies and percentages of DLTs overall and by SOC and PT will be summarized for each dose level in the Dose Escalation Phase.

All DLTs will also be presented in a data listing.

6.7.4 Clinical Laboratory Evaluation

The analyses will be performed using *Safety Population (All-treated)*.

All continuous laboratory values will be converted to Standardized International (SI) units of measure.

Summaries will be grouped by laboratory panel (e.g. hematology, blood chemistry, and urinalysis) and will be displayed for each laboratory parameter. The actual values of safety laboratory parameters and changes from baseline for each parameter will be summarized by cycle, day, and scheduled timepoints.

For those parameters where NCI CTCAE v5.0 grades are derivable, shift tables will be used to display the percentage of patients who have a shift in their laboratory grades at baseline to maximum post-baseline CTCAE severity grade. Separate summaries will be provided for parameters with bi-directional toxicity grading with “high” conditions depending on the maximum post-baseline value and the “low” conditions depending on the minimum post-baseline value.

The number and percentage of patients meeting the following concomitant criteria (i.e., suggesting a possible event meeting the Hy’s law criteria) will be provided: AST and/or ALT > 3 x upper limit normal (ULN) and concurrent elevation of total bilirubin > 2 x ULN.

All safety laboratory test results will also be presented in data listings. The safety laboratory test results which are classified as out-of-range will be presented in a separate listing. A listing of liver function tests, including flags to identify AST > 3 x ULN, ALT > 3 x ULN, concurrent elevation of total bilirubin > 2 x ULN, and results meeting Hy’s law criteria will also be presented.

A listing of pregnancy test results will also be presented.

6.7.5 Vital Sign Measurements

The analyses will be performed using *Safety Population (All-treated)*.

The vital sign (e.g. temperature, pulse, systolic and diastolic blood pressure, respiratory rate, weight, etc) actual values and mean changes from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints.

Vital signs actual values will also be presented in a data listing.

6.7.6 ECOG

The analyses will be performed using *Safety Population (All-treated)*.

ECOG performance scores and change from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints.

ECOG will also be presented in a data listing.

6.7.7 ECGs

The analyses will be performed using *Safety Population (All-treated)*.

ECG parameters and mean change from baseline will be summarized using a shift table by cycle, day, and scheduled timepoints. ECG abnormalities will be summarized by cycle, day, and scheduled timepoints. The numbers and percentages of patients with QTcF < 450 msec, between 450 and 480 msec (inclusive), > 480 msec and < 500 msec and ≥ 500 msec will also be provided by cycle, day, and scheduled timepoints.

For triplicate ECGs, the average of the available results for each parameter will be considered for summaries.

An ECG outlier analysis with numbers and percentages of patients with the following conditions will also be provided:

- Heart rate < 60 beats/min
- Heart rate < 50 beats/min
- Heart rate < 50 beats/min and concomitant $\geq 25\%$ reduction from baseline (i.e., bradycardic patient)
- Heart rate > 100 beats/min and concomitant $\geq 25\%$ increase from baseline (i.e., tachycardic patient)
- Post-baseline QT interval > 500 msec with baseline QT interval ≤ 500 msec
- Post-baseline QTcF interval > 500 msec with baseline QTcF interval ≤ 500 msec
- Post-baseline QTcF interval > 480 msec with baseline QTcF interval ≤ 480
- Post-baseline QTcF interval > 450 msec with baseline QTcF interval ≤ 450
- Patients with QTcF maximum change from baseline
 - no increase
 - $>0 - < 30$ msec
 - $\geq 30 - \leq 60$ msec
 - > 60 msec

For triplicate ECGs, the above thresholds are checked for average values (not for the three single measurements).

ECG parameters will also be presented in a data listing.

6.7.8 Extent of Exposure and Compliance

The analyses will be performed using *Safety Population (All-treated)*.

The following exposure variables will be summarized descriptively.

- Number of infusions: Total number of infusions administered, even partially.
- Total cumulative dose [REDACTED] The sum of actual doses [REDACTED] received across all cycles.

- Duration of infusion (minutes): Stop time of infusion – start time of infusion; when infusions have been interrupted, the duration of the infusion will be computed as (interruption time – start time of infusion) + (stop time of infusion - infusion resume time).

The following compliance variables will be summarized descriptively.

- Dose intensity [REDACTED]: total cumulative dose in [REDACTED]
- Expected dose intensity [REDACTED]: total cumulative planned dose during the study treatment duration in [REDACTED]

Note: If a [REDACTED] strategy is in place, this will be taken into account when deriving the expected dose intensity.

- Relative dose intensity (%): $((\text{Dose intensity}) / (\text{expected dose intensity})) \times 100$.
- Average dose per infusion [REDACTED]: Total cumulative dose [REDACTED] / (number of infusions).

The numbers and percentages of patients with missed doses, any dose modification will be summarized with their reasons. All summaries will be performed for cycle 1 and for all cycles combined, respectively.

Exposure and compliance data will also be presented in a data listing.

6.8 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.8.1 Pharmacokinetic Analysis

The analyses will be performed using *PK Population*.

Plasma concentrations (ng/mL) will be summarized by cycle, day, and scheduled time point using number of subjects, mean, standard deviation, coefficient of variation, median, minimum, and maximum. Concentrations that are below the lower limit of quantification (BLQ) before the first quantifiable concentration will be treated as zero for descriptive statistics. Below the limit of quantification values after the first quantifiable concentration will be set as missing and excluded for summary statistics.

PK parameters, including Maximum observed plasma concentration ($C_{\max}$), time to maximal concentration ($T_{\max}$), area under the concentration-time curve for a dose administration interval (AUC_{tau}), AUC_{last} , area under the concentration-time curve from time 0 to infinity (AUC_{inf}), CL, volume of distribution at steady state, and terminal half-life will be summarized by cycle, day, and scheduled time point using number of subjects, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and geometric mean CV.

PK parameters will also be summarized as described above by ADA status.

Other PK parameters may also be reported, as applicable.

Plasma concentrations and PK parameters will also be presented in data listings.

Individual and mean ($\pm$ StD) plasma concentration-time profiles plotted by dose levels, cycle, and day on both linear and semi-logarithmic scales.

Detailed pharmacokinetic analysis will be defined in a separate plan.

6.8.2 Pharmacodynamic Analysis

The analyses will be performed using *pharmacodynamics population*.

Pharmacodynamic analysis will be defined in a separate plan.

6.8.3 Immunogenicity Analysis

The analyses will be performed using *Immunogenicity Population*.

Patients who are negative for TAK-186 ADAs at baseline and become positive, who are negative at baseline and remain negative, who are positive at baseline and remain positive, who are positive at baseline and become negative, who are with unknown ADA status at baseline and become positive (if applicable), and who are unknown ADA status at baseline and become negative (if applicable) will be summarized descriptively.

Detailed immunogenicity analysis will be defined in a separate plan.

6.8.4 Biomarker Analysis

Biomarker analysis will be defined in a separate plan.

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.9.1 PRO Analysis

The analyses will be performed using *PRO analysis population*.

Items from PRO-CTCAE, FACT-Hep3, FACT-BRM3, and FACT-GP5 will be summarized descriptively as categorical variables. A score of 0, 1, 2, 3, 4 will be assigned to None/Not at all/Never, Mild/A little bit/Rarely, Moderate/Somewhat/Occasionally, Severe/Quite a bit/Frequently, and Very severe/Very much/Almost constantly, respectively. The change from baseline in scores will be summarized descriptively as continuous variable by visits. Compliance will be summarized descriptively for each questionnaire by the number of expected and number and percentage of responses received over time and overall.

6.9.2 Health Care Utilization Analysis

Not applicable.

6.10 Interim Analyses

An interim futility analysis is planned when the first 15 patients in each cohort of the cohort expansion phase become evaluable for efficacy by having at least 3 post-baseline scans or have discontinued therapy, whichever occurs earlier.

Based on Bayesian predictive probability design using ORR data, patient enrollment in each patient cohort may be stopped if the predictive probability of success given the observed interim data is less than 20%. Table c below shows the futility stopping boundaries at each interim analysis for each cohort.

Table c Futility Boundary at the Interim Analysis for Each Cohort

Patient Cohort	Number of Patients Evaluable	Minimum Number of Responders to Proceed
HNSCC	15	2
NSCLC	15	2
CRC	15	1

CRC: colorectal cancer; HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 CHANGES FROM THE PREVIOUS VERSION OF THE SAP

SAP Section	Impacted Text	Change	Rationale for Change
1.0	All		To be consistent with PA#7
2.2	All	Gated cohort expansion phase development strategy added	To be consistent with PA#7
4.0	All	Sample size in cohort expansion phase changed to 'up to approximately 210 patients'	To be consistent with PA#7
5.0	All	DLT-evaluable population definition changed to consider [REDACTED] strategy; Response evaluable population and landmark response evaluable populations removed; Immunogenicity population, pharmacodynamics population, and PRO analysis population added.	To be consistent with PA#7
6.6	The analyses will be performed using Safety Population (All-treated)	Efficacy analyses will include all patients in safety population, not only patients treated with the dose level/schedule selected for the cohort expansion phase.	To be consistent with PA#7
6.7	Separate non-CRS and CRS adverse events analyses	CRS adverse events analyses plan added	To be consistent with PA#7
6.9	PRO analysis	PRO analysis plan added	To be consistent with PA#7
6.10	All	An interim futility analysis plan added	To be consistent with PA#7

10.0 APPENDIX

10.1 Definition of Baseline

Baseline is defined as the last non-missing evaluation prior to or on the date that the first dose of the study drug is taken.

10.2 Definition of Best Overall Response

The best overall response is the best timepoint response recorded from TAK-186 infusion until the last disease assessment before a new anticancer treatment has started or the first disease progression, whichever occurs first and is defined as ‘better’ in the order of CR, PR, SD, PD, and NE. The parameters assessed based on the objective responses include ORR, DOR, DCR (defined as percentage of patients who achieve PR or CR or SD, with a duration of ≥ 2 consecutive scans), PFS, and OS. The BOR is determined once all the data for the patient are known (Eisenhauer, et al., 2009; Seymour, et al., 2017). [Table d](#) provides the BOR interpretation.

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Table d Best Overall Response When Confirmation of CR, PR and PD Are Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR ^a
PR	PR	PR
PR	SD	SD ^b
PR	PD	SD
PR	NE	SD
PD	CR	SD ^c
PD	PR	SD ^d
PD	SD	SD
PD	PD	Confirmed PD
PD	NE	Unconfirmed PD
NE	NE	NE

BOR: best overall response; CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease
 Red text represents change from RECIST v1.1 (Eisenhauer, et al., 2009).

^a. If the CR is confirmed on the next assessment, the BOR becomes a CR.

^b. If a patient has assessments that are PR, SD, then PR later without an intervening visit of PD, BOR becomes a PR.

^c. This will become a CR if a later visit > 4 weeks results in an assessment of CR with no responses of PD from an intervening visit.

^d. Will become a PR if a later visit > 4 weeks results in an assessment of PR with no responses of PD from an intervening visit.

10.3 Handling of Missing or Partial Dates

Missing or partial dates will be handled as follows:

- For time since histological or cytological diagnosis and time since diagnosis of metastatic disease, partial dates for histological or cytological diagnosis and diagnosis of metastatic disease, will be imputed as follows:
 - No imputation will be done if the year is missing.
 - If the year is before informed consent date, then missing days will be imputed as the first day of the month and missing months will be imputed as July.
 - If the year is the current year of informed consent date, then missing days will be imputed as the first day of the month and missing months will be imputed as January.

- For cancer related surgeries, partial dates will be imputed as follows: missing day of the month will be imputed as the first of the month and missing month will be imputed as January. No imputation will be done if the year is missing.
- For radiotherapies, partial dates will be imputed as follows:
 - For partially missing start dates, missing day of the month will be imputed as the first of the month and missing month will be imputed as January. No imputation will be done if the year is missing.
 - For partially missing stop dates, missing day of the month will be imputed as the last day of the month and missing month will be imputed as December and at least 1 day after the start date of the therapy. No imputation will be done if the year is missing. If, after imputation, the imputed stop date is after the death date and/or the study termination date (when available), the stop date will be imputed as the earliest of death date and study termination date.
- For Prior or Concomitant Medications: Partial start or stop dates (where UN and UNK indicate unknown day and month respectively) will be imputed as follows:
 - Start dates:
 - UN-MMM-YYYY: Impute missing day as 01, so that medications are assigned to prior and concomitant if there's any doubt.
 - DD-UNK-YYYY/UN-UNK-YYYY: If the year is before the year of first dose of study treatment, assume 01-JUL-YYYY of the collected year. If the year is after the year of first dose of study treatment, assume 01-JAN-YYYY of the collected year. If the year is the same as the year of first dose of study treatment and the stop date (after any imputation) is missing or is on or after the first dose of study treatment, then assume 01-JAN-YYYY, so that medications are assigned to prior and concomitant. If the year is the same as the year of first dose of study treatment and the stop date (after any imputation) is prior to the first dose of study treatment, then assume the stop date for the start date.
 - Stop dates:
 - UN-MMM-YYYY: Assume the last day of the month.
 - DD-UNK-YYYY/UN-UNK-YYYY: Assume 31-DEC-YYYY.
 - In case of the death/study termination of the patients and the imputed stop date is after the date of death/study termination, the stop date will be imputed as the date of death/date of study termination.
 - Completely missing dates will not be imputed.
- For adverse events (missing month is not expected; missing day is allowed): Partial start or stop dates will be imputed as follows:

- Partial start dates UN-MMM-YYYY (where UN indicates unknown day):
 - If the month and year are different from the month and year of the first dose of study drug, or the year is the same as the year of the first dose of study drug, but the month is different, it will be imputed as 01-MMM-YYYY.
 - If the month and year are the same as the first dose of study drug and the end date (after any imputation) is missing or is on or after the first dose of study drug, then it will be imputed as the date of the first dose of study drug.
 - If the month and year are the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then it will be imputed as 01-MMM-YYYY.
- Partial end dates UN-MMM-YYYY (where UN indicates unknown day):
 - UN will be imputed as the last day of the month.
 - In case of death/study termination of the patient and if the imputed end date is after the date of death/study termination, the end date will be imputed as the date of death/date of study termination.
- For CRS signs and symptoms (missing day will be imputed as above for adverse events):
Missing start or stop time will be imputed as follows:
 - Start time:
 - If the date part (after any imputation) is the same as the date part of one of the infusion date, it will be imputed as the start time of that infusion.
 - Otherwise, it will be imputed as 'T00:00'.
 - Stop time:
 - Missing stop time will be imputed as 'T23:59'.
- For death dates:
 - For partially missing death dates, missing day of the month will be imputed as the first day of the month and missing month will be imputed as January. No imputation will be done if the date is completely missing, and the imputed death dates will only be used for the overall survival analysis.
 - In case of the imputed death date is after the patient's last known alive date, the imputed death date will then be set as the patient's last known alive date.