Title: A Phase 1b Study to Evaluate TAK-659 in Combination With Nivolumab in Patients With Advanced Solid Tumors

NCT Number: NCT02834247

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C34003

A Phase 1b Study to Evaluate TAK-659 in Combination with Nivolumab in Patients with Advanced Solid Tumors
TAK-659 in Combination with Nivolumab in Advanced Solid Tumors

Phase: 1b

Version: **Final**

Date: 22JAN2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 27APR2017

1.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

2.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
BMI	body mass index
BUN	blood urea nitrogen
CLss/F	apparent oral clearance at steady state
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
FAS	full analysis set
GGT	γ-glutamyl transferase
ICH	International Conference on Harmonization
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression -free survival
PK	pharmacokinetics
PR	partial response
PTR	peak-through ratio
QOL	quality-of-life
PRO	patient-reported outcome
Rac	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease

SDB	standard database
t_{max}	first time to reach maximum plasma concentration
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

3.0 OBJECTIVES

3.1 Primary Objectives

- To determine the Maximum Tolerated Dose/Recommended Phase 2 Dose (MTD/RP2D) of TAK-659 when administered in combination with nivolumab (dose escalation phase).
- To determine the efficacy of TAK-659 plus nivolumab as measured by Overall Response Rate (ORR) (dose expansion phase).

3.2 Secondary Objectives

- To determine the safety and tolerability of TAK-659 when administered in combination with nivolumab.
- To evaluate other efficacy measures such as disease control rate (DCR) Duration of Response (DOR), rate of Progression of Disease (PD) at 6 months, progression-free survival (PFS), and Overall Survival (OS).
- To characterize the plasma pharmacokinetics (PK) of TAK-659 when administered in combination with nivolumab.

3.3 Exploratory Objectives

The exploratory objectives are:

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[redacted]

3.4 Additional Objectives

The additional objective is to collect TAK-659 plasma concentration data to contribute to population PK analyses.

3.5 Study Design

This is an open-label, multicenter, phase 1b, dose escalation study of TAK-659 in combination with nivolumab in patients with advanced solid tumors. The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2). In the dose escalation phase, the patient population will consist of all-comer patients with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: (1) patients with

metastatic triple-negative breast cancer (TNBC) who have had ≥1 prior line of chemotherapy; (2) patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed on or after a prior platinum-based chemotherapy; and (3) patients with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

It is expected that approximately 126 patients will be enrolled in the study: approximately 9 to 12 patients in the dose escalation cohort evaluating weight-based dosing of nivolumab, 3 to 6 patients in a possible nivolumab fixed-dose evaluation cohort (if it is opened), and approximately 36 patients (30 evaluable patients+15% drop off) in each of the 3 dose expansion cohorts. Enrollment is defined as the time of the initiation of the first dose of study drug. Once enrolled in the study, patients will be administered TAK-659 orally once daily (QD) during each 28-day treatment cycle. Patients receiving the combination therapy will also receive nivolumab once every 2 weeks intravenously (IV) over 60 minutes on Day 1 and Day 15 of each 28-day treatment cycle (for patients who receive 2 weeks of TAK-659 monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15). On days when both TAK-659 and nivolumab will be administered, the TAK-659 dose will be administered first followed by the nivolumab infusion (infusion to begin within 30 minutes after the TAK-659 dose). Patients, including those who achieve a complete response (CR), may receive study treatment until they experience PD or unacceptable toxicities.

The dose of nivolumab will be 3 mg/kg IV. The starting dose of TAK-659 will be 60 mg QD.

Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may be also evaluated if appropriate. Dose escalation will continue until the maximum tolerated dose (MTD) is reached, or until 100 mg QD of TAK-659 (the maximally administered dose, [MAD]) is determined to be safe and tolerable, or until a recommended phase 2 dose (RP2D), if different from the MTD or MAD, has been identified on the basis of the safety, tolerability, and preliminary pharmacokinetic (PK) and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 patients will be evaluated at the RP2D (the MTD, MAD, or a lower dose as determined) before making a decision to advance to further dose expansion.

After the combination RP2D (the MTD, MAD, or a lower dose) is determined, expansion cohorts are planned in patients with TNBC, NSCLC, and HNSCC. Thirty response-evaluable patients will be enrolled in each expansion cohort, including approximately 10 patients in each cohort who are able to provide evaluable serial biopsies.

Additionally, each expansion cohort will include 24 response-evaluable patients who are naïve to anti-programmed cell death protein 1 (PD-1)/anti-programmed cell death 1 ligand 1 (PD-L1) therapy and 6 response-evaluable patients who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable patients in each expansion cohort will first receive single-agent treatment with TAK-659 for 2 weeks at the RP2D previously determined in combination with nivolumab. Following the 2-week, single-agent treatment,

TAK-659 treatment will continue (at the same dose) in combination with nivolumab during Week 3 and beyond.

The subset of expansion patients who will be treated with single-agent TAK-659 at its combination RP2D during Weeks 1 and 2 should have accessible tumors for core or excisional biopsy and provide permission for the biopsies to be taken. These patients will undergo mandatory biopsies before single-agent TAK-659 treatment begins, at the end of the 2-week treatment window, and after 6 weeks of treatment with TAK-659 in combination with nivolumab; an optional biopsy will also be taken at the time of PD. The biopsies will be used for biomarker analysis evaluating the effect of TAK-659 on tumor cells and on immune/stromal cells supporting tumor tissue.

The remaining 20 response-evaluable patients in each expansion cohort will receive TAK-659 at its RP2D in combination with nivolumab, starting from Week 1, Day 1.

During dose escalation, serial blood samples for assessment of TAK-659 plasma PK will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15, the days on which both TAK-659 and nivolumab are administered. During the expansion phase, sparse PK samples will be collected.

All patients in the expansion cohorts will be treated until either PD or occurrence of unacceptable toxicities. The objectives of these expansion cohorts are to evaluate efficacy of TAK-659 in combination with nivolumab as measured by overall response rate (ORR) and to determine the safety and tolerability of TAK-659 in combination with nivolumab.

4.0 ANALYSIS ENDPOINTS

4.1 Primary Endpoints

- Maximum tolerated dose (MTD) or Recommended phase 2 dose (RP2D) (dose escalation phase).
- ORR as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [1] (dose expansion phase).

4.2 Secondary Endpoints

- Percentage of patients with AEs.
- Percentage of patients with Grade 3 and Grade 4 AEs.
- Percentage of patients with SAEs.
- Percentage of patients who discontinued due to AEs.
- Clinically significant laboratory values.
- Clinically significant vital sign measurements.
- Disease control rate.
- DOR.
- TAK-659 maximum (peak) plasma concentration (C_{max}), first time to reach maximum (peak) plasma concentration (t_{max}), and area under the plasma concentration versus time curve over the dosing interval (AUC_{tau}) on Cycle 1, Days 1 and 15, by dose escalation cohort.
- Rate of PD at 6 months.
- PFS.
- OS.

4.3 Exploratory endpoints

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4.4 Additional Endpoints

- TAK-659 apparent oral clearance (CL_{ss}/F), peak-trough ratio (PTR), accumulation ratio (R_{ac}), and trough concentration (C_{trough}) on Cycle 1 Day 15 by dose escalation cohort.

5.0 DETERMINATION OF SAMPLE SIZE

During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 9 to 12 dose-limiting toxicity-evaluable patients will be enrolled. The MTD/RP2D cohort will have at least 6 patients.

The sample size for the expansion cohort is estimated using a 1-sided exact binomial test at a significance level of alpha=0.1 with a power of 80%. Each cohort uses a null hypothesis of response rate ≤20%, versus an alternative hypothesis of response rate ≥40% for patients who are naïve to anti-PD/PD-L1 and any other immune-directed antitumor therapies. Therefore, approximately 24 response-evaluable patients for each cohort will be needed. In addition, 6 response-evaluable patients with prior exposure to a PD-1 or PD-L1 inhibitor will be enrolled in each expansion cohort. In total, 30 response-evaluable patients for each cohort and 90 response-evaluable patients in total (~108 patients based on a 15% drop-out rate) will be needed for all expansion cohorts.

6.0 METHODS OF ANALYSIS AND PRESENTATION

6.1 General Principles

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

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

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (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.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

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

6.2 Definition of Baseline Values

Unless otherwise specified, baseline value is defined as the last observed value before the first dose of study medication. Screening values are considered as baseline values if cycle 1 day 1 value is unavailable.

6.3 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

6.4 Conventions for Handling Missing Data

6.4.1 Conventions for Missing partial dates in Screen Visits

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

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.

2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

6.4.2 Conventions for Missing Adverse Event Dates

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

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if the month and year of the start date of the event are:
  - on or after the month and year of the date of the first dose of study drug

  and
  - on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is:
  - on or after the year of the date of the first dose of study drug

  and
  - on or before year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
- If the start date of an event is completely missing, then the event is assumed to be treatment emergent.

However, if it is clear that the end date is before the first dose of study drug, the event will not be considered treatment emergent.

6.4.3 Conventions for Missing Concomitant Medication/Therapy Dates

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

1. If the start date has a month and year but the day is missing, the event will be considered concomitant if the month and year of the start date of the event are:
   - on or after the month and year of the date of the first dose of study drug.

   and
   - on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.

2. If the start date has a year, but the day and month are missing, the event will be considered concomitant if the year of the start date of the event is:
   - on or after the year of the date of the first dose of study drug.

   and
   - on or before the year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
3. If the start date of an event is completely missing, then the event is assumed to be concomitant.

However, if it is clear that the end date is before the first dose of study drug, the event will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing, but the end date is missing completely or partially, a similar algorithm should be used to assess whether the end date is before the last dose of study drug plus 28 days to be included.

6.5 Analysis Sets

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

- Safety population: Safety population is defined as all patients who receive at least 1 dose of study drug. Patients will be analyzed according to the actual treatment they received.
- Response-Evaluable population: Response-Evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have at least 1 post-Baseline disease assessment.
- PK-Evaluable population (dose escalation): PK-Evaluable population is defined as patients with sufficient concentration-time and dosing data to reliably estimate PK parameters. This population will be used for analyses of PK parameters.
- DLT-Evaluable population: DLT-Evaluable population is defined as patients who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1) plus 2 doses of nivolumab, and observed for ≥28 days (unless DLT occurs before the end of the 28-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur.

6.6 Disposition of Subjects

Disposition of patients includes the number and percentage of patients in each dose group in the dose escalation phase, total dose escalation phase, safety expansion phase and overall for the

escalation and expansion phases, along with a summary of the primary reason for patients' study termination.

Subjects who failed the screening will be summarized in a separate table by age, age category, gender, ethnicity, race. Primary reasons for screen failure will also be summarized.

6.7 Demographic and Other Baseline Characteristics

Demographics will be summarized. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, and weight. Age will be calculated from date of birth to date of informed consent.

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

Baseline characteristics including baseline disease primary diagnosis, years since initial diagnosis, staging, Eastern Cooperative Oncology Group (ECOG) performance status, will be summarized.

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

6.8 Medication History and Concomitant Medications

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 the first dose of study treatment and through 28 days after the last dose of study medication drug, or to the start of subsequent anticancer therapy, whichever occurs first.

6.9 Study Drug Exposure and Compliance

The exposure to TAK-659 and Nivolumab will be characterized separately by: Number of Treated Cycles, Number of Cumulative Treatment Cycles ((≥1, ≥2, …, ≥6, and ≥12 cycles), Duration of Treatment (weeks) and Cumulative Dose (mg). Relative Dose Intensity (%) will be summarized for TAK-659.

Relative dose intensity (%) for TAK-659 is defined as 100 x (total dose received in mg) / (initial prescribed dose per day x number of treated days). Where number of treated days = (reference end date for study drug – reference start date for study drug) + 1.

Action on study drug will be summarized by cycles (Cycles 1, 2, 3, …6 and post-Cycle 6), and total for each dose group in the dose escalation phase, for total of the dose escalation phase, for the safety expansion phase and for overall of all the patients in the safety population.

6.10 Efficacy Analysis

All efficacy analyses will be based on investigator assessments. Investigators will assess response using the RECIST criteria for solid tumors. Efficacy endpoints will be summarized for both dose escalation and dose expansion phase. For the dose escalation phase, they will be summarized by dose groups as needed.

6.10.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is ORR in the dose expansion phase. A responder is defined as a patient who has either CR or PR. In the dose escalation phase, ORR will be summarized using the Response-Evaluable population by dose groups and the total escalation cohort. In the dose expansion phase, ORR will be summarized for the total expansion cohort and by anti-PD1/PD-L1 naïve and anti-PD1/PD-L1 relapsed/refractory subgroup.

Estimates of the ORR will be presented with 2-sided 95% exact binomial confidence intervals (CIs) as needed. Antitumor activity of TAK-659 will be based on the best overall response.

ORR will also be tabulated by baseline prognostic factors, if applicable. The prognostic factors may include, but will not be limited to, age, number and types of prior therapy. CR and PR needs to be confirmed per RECIST 1.1 guidelines to calculate ORR.

6.10.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints are DCR DOR, rate of PD at 6 months, PFS and OS.

Disease control rate (DCR) is the proportion of patients who had CR, PR, or SD. DCR will be summarized using the Response-Evaluable population. The number and percentage of patients falling into each response category (e.g., CR, PR, and SD) will be tabulated descriptively.

Rate of PD at 6 months is the proportion of patients who progressed by 6 months.

DOR is defined as the time from the date of first documentation of response to the date of first documented PD. DOR will be censored at the last response assessment that is SD or better. DOR will be censored when any of these happens: (1) patient dies without PD; (2) patient starts new anticancer therapy before PD; (3) patient drops off study due to any reason other than PD.

PFS is defined as the time from date of first study drug administration to the day of first documented PD or death due to any cause, whichever occurs first. PFS will be censored at the last response assessment that is SD or better. The detailed approach for handling missing response assessment and censoring based on US Food and Drug Administration (FDA) guidance is presented in Table 6.a.

Table 6.a Handling of Missing Response Assessment and Censoring for Progression-Free Survival Analysis Based on US Food and Drug Administration Guidance

Situation	Date of Progression of Censoring	Outcome
No baseline and/or no post baseline assessment	First dose date	Censored
Disease progression documented between scheduled visits	Date of disease progression	PFS event
No documented disease progression or death	Date of last adequate assessment*	Censored
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment*	Censored
Alternate anti-cancer therapy started prior to disease progression	Date of last adequate assessment* prior to the start of subsequent anti-cancer therapy	Censored
Death before first assessment	Date of death	PFS event
Death between adequate assessment visits	Date of death	PFS event

Abbreviation: PFS = progression-free survival.
* Adequate assessment is defined as there is sufficient radiographic data to evaluate a patient's disease status.

OS will be calculated from date of patient enrollment to the date of patient death due to any cause. Patients without documentation of death at time of the analysis will be censored as of the date the patient was last known to be alive, or the data cutoff date, whichever is earlier.

DOR, PFS, and OS will be analyzed by Kaplan-Meier approach. The corresponding KaplanMeier curves will also be plotted.

In general, time-to-event data will be analyzed by the Kaplan-Meier method and results will be summarized by the 25th, 50th, and 75th percentiles with associated 2-sided 95% CIs.

DCR, ORR, rate of PD at 6 months and DOR will be summarized using response-evaluable population for both dose escalation and dose expansion cohort, whereas PFS and OS will be summarized using safety population. For the dose escalation phase, they will be summarized by dose groups and the total escalation cohort. For the dose expansion phase, they will be summarized for the total expansion cohort and by anti-PD1/PD-L1 naïve and anti-PD1/PD-L1 relapsed/refractory subgroups.

Responses (CR and PR) need to be confirmed per RECIST 1.1 guideline to calculate any efficacy endpoints that involves CR or PR.

They will be summarized in the following groups (1) by expansion cohort (2) within each expansion cohort, by anti-PD1/PD-L1 naïve and anti-PD1/PD-L1relapsed/refractory subgroup (3) across all expansion cohorts in the anti-PF1/PD-L1 relapsed/refractory patients.

6.10.3 Additional Efficacy Endpoint(s)

{Not applicable}

6.11 Pharmacokinetic/Pharmacodynamic Analysis

{Not applicable}

6.11.1 Pharmacokinetic Analysis

The PK population will be used for the description of the plasma PK profile of TAK-659 and for the estimation of plasma PK parameters of TAK-659. Plasma concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods (LC/MS/MS).

For dose escalation cohorts, plasma TAK-659 concentrations will be summarized by time postdose and grouped by dose group and dosing cycle and day. Mean and individual plasma TAK-659 concentration data will be plotted over time and grouped by dose group and dosing cycle and day. Plasma concentration-time data will be used to calculate single-dose (Cycle 1 Day 1) and multiple-dose (Cycle 1 Day 15) plasma PK parameters of TAK-659 by noncompartmental

methods. These parameters will include, but not be limited to, C_{max}, tmax, C_{trough}, AUC_{tau} of Cycle 1 Day 1 and 15, and CLss/F, PTR, and R_{ac} of Cycle 1 Day 15. Plasma PK parameters of TAK-659 will be summarized by dose group and by dosing cycle and day.

For dose expansion cohorts, plasma concentrations of TAK-659 will be listed by cohort, nominal and actual time point, and dosing cycle and day.

TAK-659 plasma PK data from dose escalation and expansion cohorts, along with data from other studies, may contribute to population PK analyses and exposure-response analyses for pharmacodynamic, safety, and efficacy endpoints. If applicable, the specifics of the population PK and exposure-response analyses will be described in separate analysis plans, and results will be reported separately from the clinical study report.

6.11.2 Pharmacodynamic/Biomarker/Pharmacogenomic Analyses

Individual data at each time point will be summarized in a table describing changes in the course of treatment per patient. Individual and summary data also will be presented graphically for each marker. If sufficient data are generated, data may be summarized by cohort or by indication as appropriate. Descriptive statistics, graphical methods, and statistical modeling will be used as appropriate to explore the relationship between response and the levels of various biomarkers.

The relationship between observed clinical response and candidate biomarkers will be explored to identify a biomarker(s) predictive of sensitivity to TAK-659 and the combination of TAK-659 with nivolumab. Developing such a potential predictive biomarker(s) of TAK-659- and/or combination-mediated antitumor activity may require analysis of data from multiple clinical studies of TAK-659 in the future. A separate biomarker analysis plan will be written to detail such analyses.

Genotyping of polymorphisms in genes encoding proteins involved in metabolism or disposition of TAK-659 may be performed, guided by emerging understanding of the PK and clearance

mechanisms of TAK-659. Individual germline genotype will be listed for each of the polymorphisms evaluated. Descriptive and graphical methods may be used to explore the relationship between genotype and selected PK parameters for those related to the metabolism or disposition of TAK-659. Pharmacogenomic results from this study may be combined with results from future studies. These analyses may be summarized in a separate report.

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6.12 Other Outcomes

{Not applicable}

6.13 Safety Analysis

The safety analyses will be performed using the safety population.

6.13.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization.

All treatment-emergent AEs (TEAEs) will be tabulated. A TEAE for tabulation is defined as: (1) any AE that occurs after administration of the first dose of study drug and up through 28 days after the last dose of study drug or the start date of subsequent anticancer therapies, whichever comes first. AEs will be tabulated according to the MedDRA by system organ class and preferred term, and will include the following categories:

- TEAEs.
- ≥ Grade 3 TEAEs.
- Drug-related TEAEs.
- Drug-related, ≥ Grade 3 TEAEs.
- TEAEs resulting in study drug discontinuation.
- The most commonly reported TEAEs (ie, those events reported by ≥ 10% of all patients).
- Treatment-emergent SAEs.
- Nonserious TEAEs.

Patients with the same AE more than once will have the maximum intensity of that event counted within each system organ class, and once within each preferred term.

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

6.13.1.1 Serious Adverse Events

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

6.13.1.2 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 28 days of the last dose of study drug.

6.13.1.3 Adverse Events Resulting in Discontinuation of Study Drug

Treatment-emergent AEs that resulted in discontinuation of study drugs will be summarized by preferred terms. Numbers and percentages of patients in which each of the AEs resulted in study drug discontinuation will be also be summarized.

6.13.1.4 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs in Cycle 1 will be presented by dose level for patients in the DLT-evaluable population.

6.13.2 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 (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

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

The laboratory test results will be summarized for both dose escalation and dose expansion cohorts. For the dose escalation phase, they will be summarized by dose groups and by the total escalation cohort. For the dose expansion phase, they will be summarized by the total expansion cohort.

In each case, the laboratory test results will be summarized by Baseline, Post-Baseline Minimum and Post-Baseline Maximum. Change from Baseline to Post-Baseline Minimum and Change from Baseline to Post-Baseline Maximum will also be summarized.

Mean laboratory values over time will be plotted for key laboratory results. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

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

Hematology:

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)
- Lymphocytes (absolute lymphocyte count [ALC])
- Lymphocyte subsets

Serum chemistry:

- Creatinine
- Bilirubin (total)
- Lactate dehydrogenase (LDH)(with isozymes)
- Phosphate
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Amylase
- Lipase

Mean laboratory values over time will be plotted for key lab parameters, including Hb, leukocytes, ALC, ANC, platelets, and liver function tests (ALT, AST, ALP, total bilirubin), LDH (with isozymes), phosphate, creatinine, lipase and amylase).

6.13.3 Vital Signs

The actual values of vital sign parameters including oral temperature, heart rate, systolic and diastolic blood pressure, and weight, will be summarized in a similar fashion to laboratory test results.

6.13.4 12-Lead ECGs

A summary of ECG abnormalities will be presented by visit. ECG intervals (QT and Fridericia's corrected QT intervals [QTcF], PR, QRS, and heart rate) will be summarized in a similar fashion to laboratory test results.

6.13.5 Other Observations Related to Safety

Additional safety analyses may be determined at any time without prejudice to enumerate rates of toxicities and to further define the safety profile of study drugs.

6.14 Interim Analysis

There is no interim analysis planned.

6.15 Changes in the Statistical Analysis Plan

Not applicable

7.0 REFERENCES

1. 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.

Appendix

By-subject listings will be produced for the following information

1. Dispositions - dose escalation and dose expansion phases – safety population.
2. Screen failures.
3. Demographics and baseline characteristics - dose escalation and dose expansion phases – safety population.
4. Prior Therapies – dose escalation and dose expansion phases – safety population.
5. Concomitant medications – dose escalation and dose expansion phases – safety population.
6. Medical history – dose escalation and dose expansion phases – safety population.
7. RECIST response assessment – dose escalation and dose expansion phases – response-evaluable population (for this listing, a column will be added to indicate whether the subject has received treatment beyond initial RECIST-defined PD).
8. Best overall response based on investigator assessment – dose escalation and dose expansion phases – response-evaluable population.
9. Adverse events resulting in discontinuation of study drug – dose escalation and dose expansion phases – safety population.
10. Serious adverse events – dose escalation and dose expansion phases – safety population.
11. Deaths and cause of death – dose escalation and dose expansion phases – safety population.
12. Dose limiting toxicity – dose escalation phase – DLT-evaluable population.
13. Plasma concentrations of TAK-659 – dose escalation and dose expansion phases – safety population.
14. PK parameters – PK-evaluable population.
15. Significant protocol deviations.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	24-Jan-2019 15:26 UTC
	Biostatistics Approval	25-Jan-2019 02:40 UTC
	Statistical Approval	28-Jan-2019 20:17 UTC
	Biostatistics Approval	21-Feb-2019 03:23 UTC