Official Title: A Phase II, Single-Arm, Open-Label Study Evaluating the Safety and Pharmacokinetics of the Intravenous Fixed-Dose Combination (IV FDC) of Tiragolumab and Atezolizumab in Participants With Locally Advanced, Recurrent or Metastatic Solid Tumors

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF THE INTRAVENOUS FIXED-DOSE COMBINATION (IV FDC) OF TIRAGOLUMAB AND ATEZOLIZUMAB IN PARTICIPANTS WITH LOCALLY ADVANCED, RECURRENT OR METASTATIC SOLID TUMORS

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STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document V 2.0, revised 28 February 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on last page of this document	Version 4, 14 December 2023

TABLE OF CONTENTS

1. INTRODUCTION 6
   1.1 Objectives and Endpoints 6
   1.2 Study Design 8
   1.2.1 Treatment Assignment 9
   1.2.2 Data Monitoring 9
2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION 9
   2.1 Statistical Hypotheses 9
   2.2 Sample Size Determination 9
3. ANALYSIS SETS 10
4. STATISTICAL ANALYSES 10
   4.1 General Considerations 10
   4.2 Primary Endpoints Analysis 11
   4.3 Secondary Endpoints Analyses 11
   4.3.1 Pharmacokinetic Analyses 12
   4.3.2 Immunogenicity Analyses 12
   4.4 Exploratory Endpoints Analysis 13
   4.4.1 Exploratory Efficacy Analyses 13
   [redacted] 13
   [redacted] 14
   [redacted] 14
   [redacted] 14
   4.4.2 Exploratory Pharmacokinetic Analyses 15
   4.4.3 Exploratory Immunogenicity Analyses 15
   4.4.4 Exploratory Biomarker Analyses 15
   4.5 Other Safety Analyses 16
   4.5.1 Extent of Exposure 16
   4.5.2 Laboratory Data 16
   4.5.3 Vital Signs 16

4.5.4 Electrocardiograms 16
4.6 Other Analyses 16
4.6.1 Summaries of Conduct of Study 16
4.6.2 Summaries of Demographics and Baseline Characteristics 16
[redacted] 17
5. SUPPORTING DOCUMENTATION 17
6. REFERENCES 17

LIST OF TABLES

Table 1 Objectives and Endpoints 7
Table 2 Probability of Detecting One or More Adverse Events According to the Adverse Event Incidence Rate 10
Table 3 Participant Analysis Sets 10

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	complete response
CRS	cytokine release syndrome
DOR	duration of response
ECG	Electrocardiogram
FAS	full analysis set
FDC	fixed-dose combination
IMC	Internal Monitoring Committee
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rates
OS	overall survival
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PopPK	population pharmacokinetic
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
TIGIT	T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO44096 (SKYSCRAPER-11), a Phase II, single-arm, open-label study evaluating the safety and pharmacokinetics (PK) of the intravenous fixed-dose combination (IV FDC) of tiragolumab and atezolizumab in participants with locally advanced, recurrent and metastatic solid tumors. The background for the study can be found in the study protocol.

The analyses described in this SAP will supersede those specified in Protocol GO44096 for the purposes of a regulatory filing.

There are no changes to the planned analyses described in the protocol.

1.1 OBJECTIVES AND ENDPOINTS

This study's objective is to evaluate the safety, PK, and immunogenicity of tiragolumab and atezolizumab IV FDC (administered every 3 weeks [Q3W]) in participants with locally advanced, recurrent, or metastatic solid tumors. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Endpoints

Primary Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of tiragolumab and atezolizumab IV FDC	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 – The severity of CRS will also be determined according to the ASTCT CRS Consensus Grading Scale
Secondary Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of tiragolumab and atezolizumab following administration of IV FDC	• Serum concentrations of tiragolumab and atezolizumab at specified timepoints for the following parameters: – Area under the concentration-time curve at Cycle 1 – C_{max} at Cycle 1 – Additional PK parameters such as C_{min} at Cycle 1 and CL will be reported as appropriate
• To evaluate the immune response to tiragolumab and atezolizumab following IV FDC administration by measuring anti-tiragolumab and anti-atezolizumab antibodies	• Prevalence of ADAs to tiragolumab at baseline and the incidence of treatment emergent ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and the incidence of treatment emergent ADAs to atezolizumab during the study
Exploratory Objectives	**Corresponding Endpoints**
• [redacted]	• [redacted]

Primary Objective	Corresponding Endpoints
• [redacted]	• [redacted] – [redacted] – [redacted] – [redacted] – [redacted] – [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted]

ADA=anti-drug antibody; ASTCT=American Society for Transplantation and Cellular Therapy; CL=clearance; C_{max}=maximum serum concentration; C_{min}=minimum serum concentration; CR=complete response; CRS=cytokine release syndrome; DOR=duration of response; FDC=fixed dose combination; IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PD-L1=programmed death-ligand 1; PK=pharmacokinetic; PR=partial response; RECIST=response evaluation criteria in solid tumors; [redacted]; V_{ss}=volume of distribution at steady state.

1.2 STUDY DESIGN

This is a Phase II, single-arm, open-label, multicenter study designed to evaluate the safety, PK, and immunogenicity of tiragolumab and atezolizumab IV FDC administered in participants with locally advanced, recurrent, or metastatic solid tumors. Participants must have histologically-confirmed programmed death-ligand 1 (PD-L1)-selected solid tumors whose disease is locally advanced, recurrent, or metastatic and for whom an investigational agent in combination with an anti-PD-L1 antibody is considered an acceptable treatment option. Participants must not have received prior checkpoint inhibitor treatment for their cancer (CPI-Naive).

Participants receive tiragolumab 600 mg and atezolizumab 1200 mg IV FDC, administered intravenously on Day 1 of each 21-day cycle. Treatment may be continued until radiographic disease progression per investigator-assessed Response Evaluation

Criteria in Solid Tumors (RECIST) v1.1, or loss of clinical benefit, as assessed by the investigator, for participants that continue treatment after radiographic disease progression, or unacceptable toxicity.

1.2.1 Treatment Assignment

This is a single-arm, non-randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site obtains the participant's identification number from an interactive voice/web-based response system (IxRS).

1.2.2 Data Monitoring

An internal monitoring committee (IMC) evaluates cumulative safety data at regular intervals during the study, beginning with the initial safety run-in review without temporary suspension of enrollment. The safety run-in review consists of data from a minimum of the first 6 participants who have received at least one dose of study treatment and who have completed safety follow-up assessments for at least 21 days in the study. After the safety run-in review, the IMC meetings are conducted at the timepoints when the recruitment has reached approximately 20 participants and 40 participants. For each review, the participants have a minimum of 1 dose administered and be followed up for at least 21 days or discontinued from the study prior to Cycle 1 Day 21. Study team members are excluded from the IMC membership.

Further details on IMC membership, scope, frequency, and process are outlined in a separate IMC charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

2.2 SAMPLE SIZE DETERMINATION

The study is intended to obtain descriptive assessment of safety, PK, immunogenicity, efficacy, and biomarker expression in the treated population, so the sample size does not reflect explicit power and Type I error considerations.

A total sample of 40-60 participants ([redacted]) is considered sufficient and appropriate for the purposes of the study.

The primary objective of the study involves safety and tolerability of the study drug, as assessed by the incidence and severity of adverse events. The probability of observing

at least one adverse event, depending on the underlying true incidence, with the minimum sample size of 40 evaluable participants is presented in Table 2 .

Table 2 Probability of Detecting One or More Adverse Events According to the Adverse Event Incidence Rate

True Incidence of Adverse Events	Expected Probability of Detecting One or More Adverse Events (n=40)
[redacted]	

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3 .

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
Full analysis set	All enrolled study participants
Safety analysis set	All participants who received any amount of study treatment
PK-evaluable set	All participants who received any amount of study treatment and have at least one evaluable post-baseline PK assessment available.
ADA-evaluable set	All participants included in the safety analysis set who have at least one ADA assay result

ADA = anti-drug antibodies; FAS = full analysis set; PK = pharmacokinetics.

4. STATISTICAL ANALYSES

The primary analysis for this study will be performed [redacted]

4.1 GENERAL CONSIDERATIONS

All primary safety analyses, other safety analyses and the analysis of exploratory efficacy endpoints and biomarkers, unless otherwise specified, will be carried out on the safety analysis set.

Secondary and exploratory PK analyses will be performed on the PK-evaluable sets. The anti-drug antibodies (ADA)-evaluable set will be used for all the statistical analyses of immunogenicity endpoints.

In general, descriptive analyses will be carried out for all endpoints. Continuous variables will be summarized using means, standard deviations, medians, and ranges; categorical variables will be summarized using counts and percentages.

The PK analysis set will consist of all participants with at least one evaluable post-baseline PK assessment available. Consequently, no or a few data are expected to be missing, and no missing value imputation strategy is planned. Similarly, the ADA-evaluable set will also consist of all participants with at least one ADA assessment, and no missing value imputation is planned.

The baseline values are defined as the last available data obtained prior to the first dose of study treatment.

4.2 PRIMARY ENDPOINTS ANALYSIS

The primary endpoints are safety endpoints, as defined in Section 1.1 (see Table 1), which include the incidence and severity of adverse events, as assessed by the investigator, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 and also according to the American Society for Transplantation and Cellular Therapy (ASTCT) cytokine release syndrome (CRS) Consensus Grading Scale for CRS.

Safety analyses will be performed on the safety analysis set (see Section 3).

All verbatim adverse event (AE) terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation or interruption that occur on or after the first dose of study treatment or pre-existing condition that worsened on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade by means of the appropriate descriptive statistics. The investigator-assessed causality (i.e., treatment-related adverse events) will also be summarized. For events of varying severity, the highest grade will be used in the summaries. All deaths, regardless of cause, and cause of death will be summarized.

Adverse events of special interest (AESI) for the study treatment are identified by a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-Level Terms (HLTs) and Sponsor-defined adverse event grouped terms (AEGTs) from the AE clinical database by medical concept. The AESI will be summarized by NCI CTCAE grade.

4.3 SECONDARY ENDPOINTS ANALYSES

The secondary endpoints are PK and immunogenicity endpoints, as defined in Section 1.1 (see Table 1).

4.3.1 Pharmacokinetic Analyses

The PK of tiragolumab and atezolizumab IV FDC will be characterized following treatment administration. The individual exposure metrics for tiragolumab and atezolizumab IV FDC (area under the curve $[AUC]_{0\text{-}21d}$ at Cycle 1, $AUC_{0\text{-}inf}$ at Cycle 1, maximum serum concentration [C_{max}] at Cycle 1, minimum serum concentration [C_{min}] at Cycle 1, and clearance) will be derived from observed data and summarized (geometric mean, mean, SD, coefficient of variation, etc.), as appropriate.

Certain time points can be excluded from summary statistics. Reasons for exclusion of time points may include, but may not be limited to:

- Lack of Cycle 1 C_{max} PK sample (PK collection after end of infusion on Day 1 of Cycle 1),
- Lack of Cycle 1 C_{min} PK sample (PK collection between day 15 nominal time point and subsequent Cycle 2 dose or treatment discontinuation visit if discontinued before dosing).

In addition, all participants for whom the administered dose amount deviates >20% from the planned dose at Cycle 1 will be excluded from the descriptive analysis of PK parameters.

All applied exclusions for PK analysis will be reported in the Clinical Study Report (CSR).

$AUC_{0\text{-}21d}$ at Cycle 1 will also be derived from population pharmacokinetic (popPK) analysis. The use of model- predicted $AUC_{0\text{-}21d}$ at Cycle 1 is compatible with sparse sampling PK collection and to take into account of possible deviations from the protocol (i.e., sampling schedule or dosing interval) and to reduce noise (i.e., precision of analytical measurement). The popPK-derived parameters may be reported separately.

$AUC_{0\text{-}21d}$ at Cycle 1 and C_{max} at Cycle 1 will be compared descriptively with historical PK data of tiragolumab and atezolizumab following IV sequential administration and may be reported separately. Additional graphical, numerical, and exploratory statistical analysis may be conducted as appropriate.

4.3.2 Immunogenicity Analyses

The baseline prevalence of ADAs and post-baseline incidence of treatment-emergent ADAs to tiragolumab and atezolizumab will be summarized and analyzed by the appropriate descriptive statistics. Summaries will be provided separately for each molecule.

Baseline prevalence will be summarized for baseline evaluable participants, i.e. participants with an ADA assay result from a baseline sample.

Post-baseline incidence will be summarized for post-baseline evaluable participants, i.e. participants with an ADA assay result from at least one post-baseline sample. The following categories will be summarized by counts and percentages:

- Participants positive for treatment-emergent ADA: participants determined to have treatment-induced ADA or treatment-enhanced ADA during the study period
  - Treatment-induced ADA: a participant with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result
  - Treatment-enhanced ADA: a participant with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 titer unit greater than the baseline titer result
- Participants negative for treatment-emergent ADA: a participant with negative or missing baseline ADA result(s) and all negative post-baseline results, or a participant who is treatment-unaffected
  - Treatment-unaffected: a participant with positive ADA result at baseline and (a) where all post-baseline titer results are less than 0.60 titer unit greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing

For any positive sample with titer result less than the minimum reportable titer or any positive sample where the titer cannot be obtained, the titer value will be imputed as equal to the minimum reportable titer.

In addition, listings of all ADA results will be provided.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

4.4.1 Exploratory Efficacy Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.4.2 Exploratory Pharmacokinetic Analyses

[redacted]

4.4.3 Exploratory Immunogenicity Analyses

[redacted]

4.4.4 Exploratory Biomarker Analyses

[redacted]

- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will not be provided to study investigators or participants unless required by law.

4.5 OTHER SAFETY ANALYSES

Safety will also be assessed through summaries of exposure to study treatment, changes in laboratory test results and changes in vital signs and electrocardiograms (ECGs).

4.5.1 Extent of Exposure

Descriptive statistics will be presented for treatment duration, total dose received, and number of cycles.

4.5.2 Laboratory Data

Relevant laboratory data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

4.5.3 Vital Signs

Abnormal vital sign (pulse rate, respiratory rate, blood pressure, and temperature) and changes in vital signs as well as Eastern Clinical Oncology Group (ECOG) performance status will be summarized.

4.5.4 Electrocardiograms

Abnormal ECG data and changes in ECGs will be summarized. Listings of abnormal ECGs will be provided.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

The full analysis set (FAS) will be used for summaries of study conduct.

The number of participants who enroll, discontinue, or complete the study will be summarized. Reasons for treatment discontinuations and premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

4.6.2 Summaries of Demographics and Baseline Characteristics

The safety analysis set will be used for summaries of demographic and baseline characteristics.

Demographic and baseline characteristics, such as age, sex, race, weight, type of malignancy, duration of malignancy, site of metastatic disease, and so forth will be summarized using descriptive statistics and tables. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

[redacted]

[redacted]

5. SUPPORTING DOCUMENTATION

This section is not applicable since there is no additional supporting document.

6. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:2941.

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