STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB COMPARED WITH PLACEBO IN COMBINATION WITH ATEZOLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED UNRESECTABLE OR METASTATIC PD-L1–SELECTED NON–SMALL CELL LUNG CANCER**

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STUDY NAME: SKYSCRAPER-01

VERSION NUMBER: 1

ROCHE COMPOUND(S): Tiragolumab (RO7092284)
Atezolizumab (RO5541267)

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
[redacted]	
CDx	companion diagnostic
CRS	cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FPI	first patient in
GHS	global health status
HR	hazard ratio
HRQoL	health-related quality of life
IC	immune cell
IC3	immune cells $\geq$ 10%
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IL46	Item Library 46
IRF	Independent Review Facility
IxRS	interactive voice or web-based response system
MDD	minimally detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NPT	non-protocol anti-cancer therapy
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	primary analysis set
PFS	progression-free survival
PRO	patient-reported outcome
PK	pharmacokinetic
PF	physical functioning
QoL	quality of life

Abbreviation or Term	Description
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	secondary analysis set
TC	tumor cell
TC3	tumor cells ≥ 50%
TPS	tumor proportion score
TTCD	time to confirmed deterioration

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO41717 (SKYSCRAPER-01), a Phase III, randomized, double-blind, placebo-controlled study of tiragolumab, an anti-TIGIT antibody, in combination with atezolizumab compared with placebo in combination with atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–selected non–small cell lung cancer (NSCLC). The background of the study can be found in the study protocol.

1.1 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

This study will evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC, with no known epidermal growth factor receptor *(EGFR)* mutation or anaplastic lymphoma kinase *(ALK)* translocation.

The study population is selected on the basis of a high tumor tissue PD-L1 expression, as assessed by central testing, and defined by meeting at least one of the following thresholds specific to each assay: PD-L1 IHC 22C3 pharmDx assay (TPS ≥ 50%), VENTANA PD-L1 (SP142) assay (TC3 or IC3), or investigational VENTANA PD-L1 (SP263) CDx assay (TC ≥ 50%).

The primary population of interest is patients with high tumor PD-L1 expression as determined by the PD-L1 IHC 22C3 pharmDx assay (TPS ≥ 50%), hereinafter referred to as **22C3-high**.

The evaluation will also be done in patients with high tumor PD-L1 expression as determined by investigational VENTANA PD-L1 (SP263) assay (TC ≥ 50%), hereinafter referred to as **SP263-high**.

Furthermore, [redacted]

All objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
• Evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in **22C3-high** patients	• PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause
Secondary Objectives	**Corresponding Endpoints**
• Evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• PFS in SP263-high patients • OS in SP263-high patients • Confirmed ORR in 22C3-high patients, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR on two consecutive occasions ≥4 weeks apart), as determined by the investigator according to RECIST v1.1 in 22C3-high patients with measurable disease at baseline • DOR for 22C3-high patients with confirmed ORR, defined as the time from the first occurrence of a documented confirmed objective response to disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first • PFS rate at 6 months and 12 months for 22C3-high and SP263-high patients, defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and at 12 months, respectively • OS rate at 12 months and 24 months for 22C3-high and SP263-high patients, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively

ADA = anti-drug antibody; [redacted] CR = complete response; [redacted] CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for the Research and Treatment of Cancer; GHS = global health status; [redacted] IC = immune cell; IHC = immunohistochemistry; IL46 = Item Library 46; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted] QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell; TC3 = tumor cells ≥50%; TTCD = time to confirmed deterioration.

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
• Evaluate the safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE, v 5.0 – [redacted]
• Characterize the tiragolumab and atezolizumab PK profile	• Serum concentrations of tiragolumab and atezolizumab at specified timepoints
• Evaluate the immune response to tiragolumab plus atezolizumab	• Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
• Evaluate the quality of life of patients treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• TTCD in patient-reported physical functioning and GHS/QoL, as measured by EORTC QLQ-C30
[redacted]	[redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

ADA = anti-drug antibody; [redacted] CR = complete response; [redacted] CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for the Research and Treatment of Cancer; GHS = global health status; [redacted] IC = immune cell; IHC = immunohistochemistry; IL46 = Item Library 46; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted] QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell; TTCD = time to confirmed deterioration.

Table 1 Objectives and Corresponding Endpoints (cont.)

[redacted]	[redacted]
• [redacted]	• [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

ADA = anti-drug antibody; [redacted] CR = complete response; [redacted] CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for the Research and Treatment of Cancer; GHS = global health status; [redacted] IC = immune cell; IHC = immunohistochemistry; IL46 = Item Library 46; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; [redacted] QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell; TTCD = time to confirmed deterioration.

1.1.1 Expression of Objectives and Endpoint Using the Estimand Framework

Primary endpoints and key secondary endpoints are expressed using the estimand framework in Table 2, following the International Council on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

Table 2 Objectives and Estimands

Primary Objective	Estimand Definition
• Evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in 22C3-high patients	• Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC • Variable: Time from randomization to the first occurrence of the respective event of interest (as defined in Table 1) • Treatments: – Experimental: Atezolizumab 1200 mg IV Q3W followed by tiragolumab 600 mg IV Q3W and with additional medication, as required – Control: Atezolizumab 1200 mg IV Q3W followed by placebo 600 mg IV Q3W and with additional medication, as required • Intercurrent events: – Start of NPT prior to the respective event of interest – Early discontinuation from study treatment for any reason prior to the respective event of interest • Handling of intercurrent events: Treatment policy will be applied for the primary analysis • Summary measure: HR for the respective variable

CR = complete response; EORTC = European Organization for Research and Treatment of Cancer; GHS = global health status; HR = hazard ratio; NPT = non–protocol anti-cancer therapy; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q3W = every three weeks; QoL = Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

Table 2 Objectives and Estimands (cont.)

Selected Secondary Objectives	Estimand Definition
• Evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	The estimands for OS and PFS as secondary endpoints are defined similarly as for the co-primary endpoints except the following: • Population: SP263-high patients with previously untreated locally advanced unresectable or metastatic NSCLC The estimand for the secondary endpoint of confirmed ORR is defined as follows: • Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC who had measurable disease at baseline • Variable: Whether patients achieved a confirmed objective response (i.e., CR or PR on two consecutive occasions ≥ 4 weeks apart), as determined by the investigator according to RECIST v1.1 • Intercurrent events: – Start of NPT prior to the variable of interest is observed – Early discontinuation from study treatment for any reason prior to the variable of interest is observed • Handling of intercurrent events: Treatment policy with regards to the intercurrent events listed above will be applied for the analysis of confirmed ORR • Summary measure: Difference in proportions

CR = complete response; EORTC = European Organization for Research and Treatment of Cancer; GHS = global health status; HR = hazard ratio; NPT = non–protocol anti-cancer therapy; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q3W = every three weeks; QoL = Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

Table 2 Objectives and Estimands (cont.)

Selected Secondary Objectives (cont.)	Estimand Definition (cont.)
• Evaluate the quality of life of patients treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab	The estimand for the secondary endpoint of TTCD is defined similarly as for the primary endpoints in terms of population and treatments; the other attributes are defined as follows: • Variable: Time from randomization until the first confirmed clinically meaningful deterioration on physical functioning and GHS/QoL EORTC QLQ-C30 select scales; confirmed clinically meaningful deterioration is defined as a clinically meaningful decrease from baseline that must be held for at least two consecutive assessments or an initial clinically meaningful decrease from baseline followed by death from any cause within 6 weeks • Intercurrent events: – Start of NPT prior to a confirmed clinically meaningful deterioration – Early discontinuation from study treatment for any reason prior to a confirmed clinically meaningful deterioration – Death that occurs before patients report any clinically meaningful deterioration • Handling of intercurrent events: Treatment policy with regards to the start of NPT and early discontinuation; and while-on-treatment/while-alive strategy for death will be applied for the TTCD analysis • Summary measure: HR for TTCD

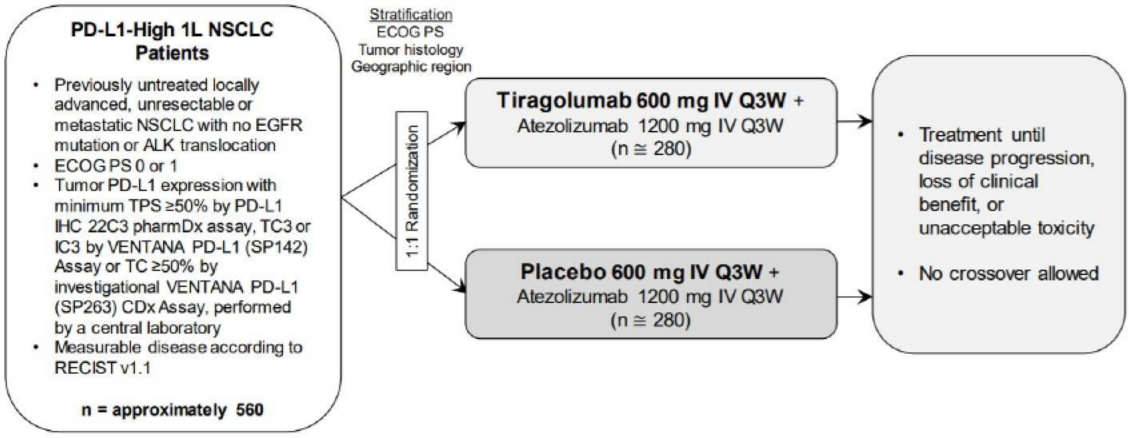
CR = complete response; EORTC = European Organization for Research and Treatment of Cancer; GHS = global health status; HR = hazard ratio; NPT = non–protocol anti-cancer therapy; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q3W = every three weeks; QoL = Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

1.2 STUDY DESIGN

This is a Phase III, randomized, double-blinded, placebo-controlled, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced, unresectable or metastatic PD-L1–selected NSCLC.

The study schema is shown in Figure 1.

Figure 1 Study Design



1L = first-line; *ALK* = anaplastic lymphoma kinase (gene); CDx = companion diagnostic; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor gene; IC = immune cell; IC3 = immune cells ≥ 10%, IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; PAS = primary analysis set; PS = Performance Status; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TC = tumor cell; TC3 = tumor cells ≥ 50%, TPS = tumor proportion score.

Note: Approximately 560 patients with previously untreated, locally advanced unresectable or metastatic NSCLC that harbors high tumor PD-L1 expression, as assessed by central testing, using any of the three assays, TPS ≥ 50% by PD-L1 IHC 22C3 pharmDx assay, TC3 or IC3 by VENTANA PD-L1 (SP142) assay, or TC ≥ 50% by investigational VENTANA PD-L1 (SP263) CDx assay, will be enrolled globally. [redacted]

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression by a central laboratory using the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay, VENTANA PD-L1 (SP142) Assay, and the investigational VENTANA PD-L1 (SP263) Companion Diagnostic (CDx) Assay. Only patients with high tumor PD-L1 expression by any of the three assays will be enrolled globally: tumor proportion score (TPS) ≥ 50% using the 22C3 pharmDx assay, tumor cells ≥ 50% [TC3] or immune cells ≥ 10% [IC3] using the VENTANA (SP142) Assay, or TC ≥ 50% using the investigational VENTANA (SP263) CDx Assay.

Eligible patients will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), tumor histology (non-squamous vs. squamous), and geographic region of the enrolling site (Asia vs. non-Asia). Eligible patients will be randomized in a 1:1 ratio to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab.

In the experimental arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle,

followed by tiragolumab at a fixed dose of 600 mg administered to patients by IV infusion Q3W on Day 1 of each 21-day cycle.

In the control arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Treatment may be continued as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for disease progression per Response Evaluation Criteria for Solid Tumors, Version 1.1 (RECIST v1.1) will be permitted to continue study treatment (tiragolumab plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria specified in study protocol Section 3.1.1 and provide written consent.

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays (see study protocol Section 4.5.6 and Appendix 1). After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[redacted]

After completion of the global enrollment phase, [redacted]

[redacted]

1.2.1 Treatment Assignment and Blinding

This is a Phase III, randomized, double-blinded, placebo-controlled study. After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by central testing), the study site will obtain the patient's identification number and blinded treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomized to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab. Randomization will occur in a 1:1 ratio through the use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- ECOG Performance Status (0 vs. 1)
- Tumor histology of NSCLC (non-squamous vs. squamous)
- Geographic region of the enrolling site (Asia vs. non-Asia)

Patients should receive their first dose of study drug on the day of randomization if possible. [redacted]

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, [redacted]

1.2.2 Independent Review Facility

All primary imaging data used for tumor assessments will be collected by the Sponsor and a centralized, blinded independent review by an Independent Review Facility (IRF) may be conducted.

1.2.3 Data Monitoring

An iDMC will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC's roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months from the time of enrollment of the first patient. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

2. STATISTICAL HYPOTHESES

The purpose of this study is hypothesis testing and estimation regarding the effect of tiragolumab in combination with atezolizumab on the duration of PFS and/or OS compared with placebo plus atezolizumab.

The primary and the key secondary objectives of this study are to evaluate the efficacy of tiragolumab in combination with atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic NSCLC and high tumor PD-L1 expression as determined by the 22C3 pharmDx assay (TPS $\geq$ 50%) or by the investigational VENTANA (SP263) CDx assay (TC $\geq$ 50%), defined as the PAS and secondary analysis set (SAS), respectively (see Section 4).

The null (H_0) and alternative (H_1) hypotheses regarding PFS or OS in the PAS or SAS can be phrased in terms of the population hazard ratio (HR) λ between the experimental arm and the control arm:

$$H_0: \lambda = 1 \text{ versus } H_1: \lambda \neq 1$$

3. SAMPLE SIZE DETERMINATION

The co-primary endpoints of PFS and OS will be analyzed in the PAS. The study will enroll approximately 500 patients in the PAS. [redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.2 CO-PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL IN THE PRIMARY ANALYSIS SET

The primary analysis of the co-primary endpoint of PFS in the PAS will occur when approximately [redacted] PFS events [redacted] patients) or approximately [redacted] OS events ([redacted] patients) have been observed in this analysis set, whichever occurs later. The [redacted] PFS events provides a [redacted] power to detect a target HR of [redacted] for PFS at a two-sided significance level of [redacted] based on the following assumptions:

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

[redacted]

[redacted]

[redacted]

3.3 CO-PRIMARY ENDPOINT: OVERALL SURVIVAL IN THE PRIMARY ANALYSIS SET

The final analysis of the co-primary endpoint of OS will occur when approximately [redacted] deaths ([redacted]) have been observed in the PAS. This provides an [redacted] power to detect a target HR of [redacted] for OS at a two-sided significance level of [redacted] based on the following assumptions:

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. ANALYSIS SETS

The analysis sets are defined in Table 4.

Table 4 Analysis Sets

Analysis Set	Definition
FAS	All randomized patients, regardless of whether patients received the assigned treatment
PAS	All randomized patients with high tumor PD-L1 expression, as determined by the 22C3 pharmDx assay (TPS ≥ 50%)
SAS	All randomized patients with high tumor PD-L1 expression, as determined by the investigational VENTANA SP263 assay (TC ≥ 50%)
[redacted]	
Safety-evaluable set	All randomized patients who received at least one dose of study treatment
PK-evaluable set	All patients who received any dose of study treatment and who have at least one post-baseline PK sample available
Atezolizumab ADA-evaluable set	All patients who received at least one dose of atezolizumab treatment and with an ADA assay result from at least one sample result
Tiragolumab ADA-evaluable set	All patients who received at least one dose of tiragolumab treatment and with an ADA assay result from at least one sample result

ADA = anti-drug antibody; FAS = full analysis set; [redacted] PAS = primary analysis set; PK = pharmacokinetic; SAS = secon [redacted] TPS = tumor proportion score.

5. STATISTICAL ANALYSES

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

5.1 GENERAL CONSIDERATIONS

PFS and OS will be performed in the PAS and SAS, and other efficacy endpoints will be analyzed in the PAS, unless otherwise specified. Patients will be analyzed according to the treatment assigned at randomization by IxRS.

Safety analyses will be conducted on the safety-evaluable set, unless otherwise specified. Patients will be analyzed according to the treatment they actually received. Specifically, a patient will be included in the tiragolumab plus atezolizumab arm in the safety analyses if the patient receives any amount of tiragolumab, regardless of the initial treatment assignment at randomization.

Unless otherwise stated, baseline values are the last available data obtained prior to the patient receiving the first dose of study treatment on Cycle 1, Day 1 (or at screening, for patients who were not treated).

5.2 PATIENT DISPOSITION

Study enrollment and reasons for discontinuation from the study will be summarized by treatment arm for the FAS. Study treatment disposition and reasons for discontinuation from study treatment will be summarized for the safety-evaluable set.

5.3 PRIMARY ENDPOINTS ANALYSIS

5.3.1 Definition of Co-Primary Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator according to RECIST v1.1 and OS in the PAS.

[redacted]

5.3.1.1 Progression-Free Survival

The estimand for the co-primary endpoint of PFS is defined as follows:

- Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC
- Variable: Time from randomization to the first documented disease progression as determined by the investigator with the use of RECIST v1.1 or death from any cause, whichever occurs first
- Treatments:
  - Experimental: Atezolizumab 1200 mg IV Q3W followed by tiragolumab 600 mg IV Q3W and with additional medication, as required
  - Control: Atezolizumab 1200 mg IV Q3W followed by placebo 600 mg IV Q3W and with additional medication, as required

- Intercurrent events:
  - Start of non-protocol anti-cancer therapy (NPT) prior to a PFS event
  - Early discontinuation from study treatment for any reason prior to a PFS event
- Handling of intercurrent events: Treatment policy will be applied for the primary analysis
- Summary measure: HR for PFS

Patients who have not experienced disease progression and have not died at the time of analysis will be censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

5.3.1.2 Overall Survival

The estimand for the co-primary endpoint of OS is defined as follows:

- Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC
- Variable: Time from randomization to death from any cause
- Treatments:
  - Experimental: Atezolizumab 1200 mg IV Q3W followed by tiragolumab 600 mg IV Q3W and with additional medication, as required
  - Control: Atezolizumab 1200 mg IV Q3W followed by placebo 600 mg IV Q3W and with additional medication, as required
- Intercurrent events:
  - Start of NPT
  - Early discontinuation from study treatment for any reason
- Handling of intercurrent events: Treatment policy with regards to the intercurrent events listed above will be applied for the primary analysis
- Summary measure: HR for OS

Patients who have not died at the time of analysis will be censored at the date when they were last known to be alive. Patients with no post-baseline information will be censored at the date of randomization.

5.3.2 Main Analytical Approach for Co-Primary Endpoints

The stratified log-rank test will be used to compare PFS and OS between the treatment arms, according to the protocol-defined stratification factors as entered in IxRS for the PAS.

Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least one stratum (i.e., a combination of stratification factor levels across ECOG Performance Status [0 vs 1, tumor histology [non-squamous vs. squamous] and geographic region of the enrolling site [Asia vs. non-Asia] per IxRS) has fewer than 10 OS events, the stratification factor that contains the level with the smallest number of patients will be

removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with fewer than 10 OS events. The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

Cox proportional hazards model, stratified by the protocol-defined stratification factors as entered in IxRS, will be used to estimate the HR between the two treatment arms and its 95% CI. Kaplan-Meier methodology will be used to estimate median PFS and OS and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS (Brookmeyer and Crowley 1982).

5.3.3 Handling of Missing Data

5.3.3.1 Progression-Free Survival

The impact of missing scheduled tumor assessments on PFS will be assessed depending on the number of patients who missed tumor assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff. The following two sensitivity analyses will be performed:

- Patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff will be censored at the last tumor assessment prior to the missed visits.
- The impact of missing scheduled tumor assessments on PFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis method.

To apply the interval censoring, for each patient, the left and the right boundaries of the interval will be derived based on the rules shown in Table 5:

Table 5 Censoring Boundaries for PFS Sensitivity Analyses

Situations	Left Boundary [a]	Right Boundary
Patients who had disease progression prior to death	The date of the last assessment that showed a progression-free status	The date of the first assessment that showed disease progression
Patients who died without disease progression	The date of the last assessment that showed a progression-free status	Death date
Patients who did not die nor had disease progression	The date of the last assessment that showed a progression-free status	Not applicable (Missing)

[a] For patients who did not have any post-baseline assessment with progression-free status, the left boundary is the date of randomization.

The PFS survival curves will be estimated using the nonparametric maximum likelihood estimate (NPMLE; Turnbull 1974) for each treatment arm. The median PFS of each

treatment arm will be reported and its 95% CI will be constructed based on the Brookmeyer-Crowley method (Brookmeyer and Crowley 1982).

Stratified log-rank test proposed by Sun (Sun 1996) will be used to compare PFS between the treatment arms. The treatment effect will be estimated using a stratified proportional hazard regression model (Finkelstein 1986) with a parametric assumption of piecewise exponential distribution for the baseline hazard function (Friedman 1982, Royston and Parmar 2002).

5.3.3.2 Overall Survival

Patients who are lost to follow-up will be censored at the last date they were known to be alive for the primary analysis of OS. If $>5\%$ of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between the two treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

5.3.4 Sensitivity Analyses for Co-Primary Endpoints

Sensitivity analyses of the primary endpoints will be performed to assess the impact of stratification. These analyses will follow the same analysis methods as the primary endpoints, with the exception that PFS and OS will be compared using an unstratified log-rank test and the HR will be estimated from unstratified Cox regression hazard model (see also Section 5.3.2).

If at the time of the primary analysis for PFS, the observed PFS events in PAS are more than 10% over the protocol-specified events of [redacted], a sensitivity analysis using an earlier data cutoff date with targeted [redacted] events will be performed.

When the clinical effect is delayed by $>20\%$ of the median OS of the control group (e.g., providing the observed median OS of the control group is [redacted], it means the observed KM curve does not separate until [redacted], a sensitivity analysis of OS may be performed using the weighted log-rank test based on the Rho-Gamma weight function family (Fleming and Harrington 1991) or piece-wise linear weight functions (Lin and Leon 2017) that weigh more heavily on late events to account for the delayed clinical effect (Fine 2007). In addition, HR estimates based on the corresponding Cox model (Lin and Leon 2017) using the piece-wise linear weight functions may also be provided to enhance clinical interpretation of the treatment effect that varies over time.

5.3.5 Supplementary Analyses for Co-Primary Endpoints

The following supplementary analyses will be performed for the co-primary efficacy endpoints of PFS and OS in which a different handling rule of intercurrent events is implemented to provide further understanding of the treatment effect.

To assess the impact of the intercurrent event of starting an NPT prior to a PFS event, the primary analysis of PFS will be repeated with such intercurrent event handled using

a hypothetical strategy if > 5% of patients received NPT prior to a PFS event in either treatment arm. To estimate the estimand that implements this strategy, patients who start an NPT before a PFS event will be censored at the time of the last tumor assessment before the initiation of NPT.

To assess the impact of the intercurrent event of starting an NPT on OS, the primary analysis of OS will be repeated with such intercurrent event handled using a hypothetical strategy if > 10% of patients received NPT in either treatment arm. Rank-preserving structural failure time method will be used to provide an estimate of the OS time for the treatment arms had NPT not been received (Robins and Tsiatis 1991). This method estimates OS measured from the time of NPT by applying an estimate of the benefit of the NPT. The total OS time (sum of time to NPT and the estimated survival time after NPT is started) will then be analyzed using the same methodology as for the primary analysis of OS.

5.3.5.1 Subgroup Analyses for Co-Primary Endpoints

The generalizability of OS and PFS results when comparing the experimental arm to the control arm will be investigated by estimating the treatment effect in subgroups defined by demographics (e.g., age, sex, race/ethnicity, and geographic region of the enrolling site) and baseline prognostic characteristics (e.g., ECOG Performance Status and histology). Summaries of OS and PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median PFS and OS, will be provided in forest plots.

5.4 SECONDARY ENDPOINTS ANALYSES

5.4.1 Key/Confirmatory Secondary Endpoints

5.4.1.1 Progression-Free Survival and Overall Survival in the Secondary Analysis Set

The estimands of the secondary endpoints of PFS and OS are defined similarly as for the co-primary endpoints of PFS and OS in Section 5.3.1 with the exception of the following:

- Population: SP263-high patients with previously untreated locally advanced unresectable or metastatic NSCLC

The same analytical approaches for the primary analysis of PFS and OS specified in Section 5.3 will be used to analyze PFS and OS in the SAS.

5.4.1.2 Confirmed Objective Response Rate

The estimand for the confirmed objective response rate (ORR) is defined as follows:

- Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC who had measurable disease at baseline.

- Variable: Whether patients achieved a confirmed objective response (i.e., complete response or partial response on two consecutive occasions ≥4 weeks apart), as determined by the investigator according to RECIST v1.1
- Treatments:
  - Experimental: Atezolizumab 1200 mg IV Q3W followed by tiragolumab 600 mg IV Q3W and with additional medication, as required
  - Control: Atezolizumab 1200 mg IV Q3W followed by placebo 600 mg IV Q3W and with additional medication, as required
- Intercurrent events:
  - Start of NPT prior to a confirmed objective response is observed
  - Early discontinuation from study treatment for any reason prior to a confirmed objective response is observed
- Handling of intercurrent events: Treatment policy with regards to the intercurrent events listed above will be applied
- Summary measure: Difference in proportions of patients achieved confirmed objective response between treatment arms

Confirmed ORR will be analyzed in patients with measurable disease at baseline and compared between treatment arms using the stratified Cochran Mantel-Haenszel test. The 95% CI for the difference in confirmed ORRs between the two treatment arms will be computed using the Newcombe method. The 95% CI of the confirmed ORR will be calculated for each treatment arm using the Wilson score method.

5.4.2 Supportive Secondary Endpoints

5.4.2.1 Duration of Response

Duration of response (DOR) will be assessed in the PAS with patients who achieved a confirmed objective response, as determined by the investigator according to RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a confirmed objective response until the first date of progressive disease as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. DOR will be based on a non-randomized subset of patients (specifically, patients who achieve a confirmed objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Median DOR and corresponding 95% CIs will be estimated using Kaplan-Meier methodology for each treatment arm.

5.4.2.2 Progression-Free Survival and Overall Survival Rates at Selected Timepoints

The PFS rates at 6 months and at 12 months are defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and 12 months after

randomization. The PFS rates will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated using the normal approximation method, with standard errors computed using Greenwood's method.

Similar analyses will be performed for the OS rates at 1 and 2 years, defined as the proportion of patients who have not died from any cause at 12 months and 24 months after randomization.

5.4.2.3 Time to Confirmed Deterioration in Physical Functioning and Global Health Status

Patient-reported physical functioning (PF) (Items 1–5) and global health status (GHS)/quality of life (QoL) (Items 29–30) are collected and measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. A high score for the physical function subscale represents a high/healthy level of functioning and a high score for the GHS/QoL subscale represents a high health-related quality of life. Both scales will be linearly transformed so that each score will range from 0 to 100. A score change of at least 10 points in GHS/QoL and PF scale score is perceived by patients as clinically meaningful deterioration (Osoba et al. 1998).

The estimand for time to confirmed deterioration (TTCD) in PF and GHS/QoL, respectively, are defined as the follows:

- Population: 22C3-high patients with previously untreated locally advanced unresectable or metastatic NSCLC
- Variable: Time from randomization until the first confirmed clinically meaningful deterioration on PF and GHS/QoL EORTC QLQ-C30 scales; confirmed clinically meaningful deterioration is defined as a clinically meaningful decrease from baseline that must be held for at least two consecutive assessments or an initial clinically meaningful decrease from baseline followed by death from any cause within 6 weeks
- Treatments:
  - Experimental: atezolizumab 1200 mg IV Q3W followed by tiragolumab 600 mg IV Q3W and with additional medication, as required
  - Control: atezolizumab 1200 mg IV Q3W followed by placebo 600 mg IV Q3W and with additional medication, as required
- Intercurrent events:
  - Start of NPT prior to a confirmed clinically meaningful deterioration
  - Early discontinuation from study treatment for any reason prior to a confirmed clinically meaningful deterioration
  - Death that occurs before patients report any clinically meaningful deterioration

- Handling of intercurrent events: A treatment-policy strategy with regards to the start of NPT and early discontinuation; and while-on-treatment/while-alive strategy for death will be applied for the TTCD analysis
- Summary measure: HR for TTCD

For patients who discontinue study treatment for radiographic disease progression per RECIST v1.1 and enter the survival follow-up, the questionnaires will be completed at 3 months (±30 days) and 6 months (±30 days) following radiographic disease progression per RECIST v1.1. Patients who have not experienced a confirmed clinically meaningful deterioration by the data cutoff date will be censored at the last time they complete an assessment. Patients with no baseline or post-baseline assessment will be censored at the date of randomization. According to the while-on-treatment/while-alive strategy, patients who die before reporting any clinical meaningful deterioration will be censored at the last time they complete an assessment. TTCD will be analyzed using the same methods as for the co-primary endpoint of PFS.

[redacted]

[redacted]

5.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the safety-evaluable set (see Section 4), with patients grouped according to whether any tiragolumab treatment was received.

5.6.1 Extent of Exposure

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized by each treatment arm and for each study drug with descriptive statistics.

5.6.2 Adverse Events

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Severity for all adverse events will be

graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, [redacted]

All treatment-emergent adverse events will be summarized by treatment arm and NCI CTCAE grade. [redacted] In addition, common adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), AEs leading to study treatment discontinuation or interruption, Grade 3-4 AEs, and fatal AEs (Grade 5) will be summarized accordingly. For the purpose of analyses, AEs of special interest (AESIs) will be identified by a set of comprehensive definitions using standardized MedDRA queries, high-level terms and Sponsor-defined adverse event grouped terms from the clinical database and presented by medical concepts. AESIs will be summarized by treatment arm and CTCAE grade.

Multiple occurrences of the same event will be counted once at the maximum severity.

For the safety analyses, “treatment-emergent” is defined as adverse events occurring on or after the first dose of study drug treatment or as a pre-existing condition that worsened on or after the first dose of the study treatment up to the data cutoff date.

Listings of AEs will include all treatment emergent adverse events up to the data cutoff date.

Deaths during the study treatment period and those reported during the follow-up period and causes of death will be summarized by treatment arm.

5.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized descriptively. Shift tables from baseline to worst value post-baseline will also be presented.

5.6.4 Vital Signs

Vital signs will be summarized by treatment arm and visit.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

Study enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria will be summarized by treatment arm for the FAS.

5.7.2 Summaries of Treatment Group Comparability

Demographic characteristics (age, sex, race/ethnicity), baseline disease characteristics (e.g. smoking status) and stratification factors (ECOG Performance Status, tumor

histology, and geographic region of the enrolling site) will be summarized overall and by treatment arm for the PAS.

Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

5.7.3 Pharmacokinetic Analyses

Tiragolumab and atezolizumab serum concentration data (minimum serum concentration [C_{min}] and maximum serum concentration [C_{max}]) will be tabulated and summarized. Descriptive statistics will include arithmetic and geometric means, medians, ranges, and standard deviations, as appropriate.

Additional pharmacokinetic (PK) analyses will be conducted, as appropriate, based on the availability of data.

5.7.4 Immunogenicity Analyses

The immunogenicity analyses will include patients with any tiragolumab and/or atezolizumab anti-drug antibody (ADA) assessments, with patients grouped according to the treatment received.

The number and proportion of treatment-emergent tiragolumab ADA-positive patients will be summarized for the experimental arm. The number and proportion of treatment-emergent atezolizumab ADA-positive patients will be summarized by the treatment arm.

Demographic and baseline characteristics, pharmacokinetics, efficacy, and safety by treatment-emergent tiragolumab and atezolizumab ADA subgroups may be reported.

Immunogenicity analyses will be conducted on the atezolizumab and tiragolumab ADA-evaluable sets.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

a [redacted]

[redacted]

[redacted]

a [redacted]

b [redacted]

6. SUPPORTING DOCUMENTATION

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

7. REFERENCES

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