Official Title: A Phase III, Open-Label, Randomized Study of Atezolizumab and Tiragolumab Compared with Durvalumab in Patients with Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer who have not Progressed after Concurrent Platinum-Based Chemoradiation

NCT Number: NCT04513925

Document Date: Statistical Analysis Plan Version 1: 07-Oct-2024

STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB AND TIRAGOLUMAB COMPARED WITH DURVALUMAB IN PATIENTS WITH LOCALLY ADVANCED, UNRESECTABLE STAGE III NON–SMALL CELL LUNG CANCER WHO HAVE NOT PROGRESSED AFTER CONCURRENT PLATINUM-BASED CHEMORADIATION (SKYSCRAPER-03)**

STUDY NUMBER: GO41854

STUDY NAME: SKYSCRAPER-03

VERSION NUMBER: 1

ROCHE COMPOUNDS: Tiragolumab (RO7092284)
Atezolizumab (RO5541267)

EUDRACT NUMBER: 2019-002925-31

IND NUMBER: 129258

NCT NUMBER: NCT04513925

PLAN PREPARED BY: [redacted], M.S.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 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 8.0, 21 September 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ASTCT	American Society for Transplantation and Cellular Therapy
CDx	companion diagnostic
CI	confidence interval
CRT	chemoradiotherapy
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
FAS	Full Analysis Set
GHS	global health status;
HR	hazard ratio
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
iDCC	independent Data Coordinating Center
IL46	item list 46
INV	investigators
IRF	Independent Review Facility
IV	intravenous
IxRx	interactive voice/web-based response system
MDD	minimally detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPT	non-protocol anti-cancer therapy
NSCLC	non-small cell lung cancer
OS	overall survival
ORR	objective response rate
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PPAS	programmed death-ligand 1-positive analysis set

PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
TC	tumor cell
TTCD	time to confirmed deterioration
TTDM	time to death or distant metastasis

1. INTRODUCTION

Study GO41854 (SKYSCRAPER-03) is a Phase III, open-label, randomized, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab compared with durvalumab administered to patients with locally advanced, unresectable Stage III non-small cell lung cancer (NSCLC) who have not progressed following concurrent platinum-based chemoradiotherapy (CRT) as consolidation therapy. The background for the study can be found in the study protocol. The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol GO41854 for the purposes of a regulatory filing.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Primary endpoints and key secondary endpoints are expressed in Table 1 using the estimand framework, in accordance with the International Conference on Harmonization (ICH) E9 (R1) statistical principles for clinical trials (ICH 2020). Table 2 presents the remaining objectives and corresponding endpoints.

In this SAP, "study treatment" refers to the combination of treatments assigned to patients as part of this study and includes tiragolumab, atezolizumab, and durvalumab.

Table 1 Primary and Key Secondary Objectives and Corresponding Estimands

Primary Objectives	Estimand Definition
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the programmed death–ligand 1-positive analysis set (PPAS)	PFS, as assessed by an IRF. The estimand is defined as follows: • Population: patients with locally advanced, PD-L1 positive [redacted] unresectable Stage III non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation (hereafter referred to as the PPAS) • Endpoint: time from randomization to the first occurrence of disease progression, as determined by the IRF according to RECIST v1.1, or death from any cause, whichever occurs first • Treatment: – Tiragolumab plus atezolizumab: atezolizumab (1680 mg by IV infusion), followed by tiragolumab (840 mg by IV infusion) on Day 1 of each 28-day cycle for a maximum of 13 cycles – Durvalumab: durvalumab 10 mg/kg (by IV infusion) every two weeks (Q2W) on Days 1 and 15 of each 28-day cycle for a maximum of 13 cycles, or fixed dose durvalumab at 1500 mg (by IV infusion) every four weeks (Q4W) on Day 1 of each 28-day cycle for a maximum of 13 cycles • Intercurrent events and handling strategies: – Early discontinuation from study treatment from any cause prior to the respective event of interest: treatment policy strategy – Start of non-protocol anti-cancer therapy prior to the respective event of interest: treatment policy strategy • Population-level summary: hazard ratio for PFS
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the full analysis set (FAS)	PFS, as assessed by an IRF. The estimand is defined in the same way as PFS in the PPAS, except: • Population: patients with locally advanced, unresectable Stage III non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation (hereafter referred to as the FAS)

Key Secondary Objectives	Estimand Definition
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	OS, where the estimand is defined in the same way as for PFS, except: • Endpoint: time from randomization to death from any cause • Population-level summary: hazard ratio for OS
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	PFS, as assessed by the investigator. The estimand is defined in the same way as for IRF-assessed PFS, except: • Endpoint: 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
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	Confirmed ORR, as assessed by an IRF. The estimand is defined as follows: • Population: patients with measurable disease at baseline, as determined by an IRF • Endpoint: whether patients achieved a confirmed objective response (i.e., CR or PR on two consecutive occasions $\geq$4 weeks apart), as determined by the IRF according to RECIST v1.1 • Treatment: as described above • Intercurrent events and handling strategies: as described above • Population-level summary: difference in proportions between treatment arms
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	Confirmed ORR, as assessed by the investigator. The estimand is defined in the same way as for IRF-assessed ORR, except that ORR is determined by the investigator.
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	DOR, as assessed by an IRF. The estimand is defined as follows: • Population: patients with a confirmed response, as determined by an IRF • Endpoint: time from the date of the first occurrence of a confirmed objective response until the first date of progressive disease, as determined by an IRF according to RECIST v1.1, or death from any cause, whichever occurs first • Treatment: as described above • Intercurrent events and handling strategies: as described above • Population-level summary: median for DOR

Key Secondary Objectives (continued)	Estimand Definition (continued)
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS	DOR, as assessed by the investigator. The estimand is defined in the same way as for IRF-assessed DOR, except that DOR is determined by the investigator.
To evaluate the quality of life of patients treated with tiragolumab plus atezolizumab compared with durvalumab in the PPAS	TTCD, with the estimand defined similarly as for the primary endpoints in terms of population and treatments; the other attributes are defined as follows: • Endpoint: the time from the date of randomization until the first confirmed clinically meaningful deterioration on each respective score. Confirmed clinically meaningful deterioration in symptoms using the EORTC QLQ-LC13 is defined as a clinically meaningful increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial clinically meaningful increase from baseline followed by death from progressive disease. Confirmed clinically meaningful deterioration in GHS and physical functioning using EORTC QLQ-C30 is defined as a clinically meaningful decrease from baseline in GHS or physical functioning scale score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death due to progressive disease. • Intercurrent events and handling strategies: – Early discontinuation from study treatment from any cause prior to the respective event of interest: treatment policy strategy – Start of non-protocol anti-cancer therapy prior to the respective event of interest: treatment policy strategy – Death that occurs before patients report any clinically meaningful deterioration: treatment policy strategy • Population-level summary: hazard ratio for TTCD
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the FAS	The estimands for the efficacy objectives in the FAS are defined in the same way as for the PPAS.
To evaluate the quality of life of patients treated with tiragolumab plus atezolizumab compared with durvalumab in the FAS	The estimand for TTCD in the FAS is defined in the same way as for the PPAS.

Note: Primary and secondary endpoints are expressed using the estimand framework following the International Conference on Harmonisation E9 (R1).

CDx = companion diagnostic; CR = complete response; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; GHS = global health status; IRF = Independent Review Facility; IV = intravenous ORR = objective response rate; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TC = tumor cell; TTCD = time to confirmed deterioration; TTDM = time to distant metastasis.

Table 2 Other Secondary and Exploratory Objectives and Endpoints

Other Secondary Objectives	**Corresponding Endpoints**
To evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab in the PPAS and the FAS	• PFS rate at 12, 18, and 24 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 12, 18, and 24 months, as determined by an IRF and investigator according to RECIST v1.1 • OS rate at 12, 24, 36, and 48 months, defined as the proportion of patients who have not experienced death from any cause at 12, 24, 36, and 48 months • TTDM, defined as the time from the date of randomization until the date of first documented distant metastasis, as assessed by investigator according to RECIST v1.1, or death, whichever occurs first. Distant metastasis is defined as any new lesion that is outside of the radiation field.
To evaluate the safety and tolerability of tiragolumab plus atezolizumab compared with durvalumab	• Incidence and severity of adverse events with severity graded according to the NCI CTCAE v5.0 Severity for CRS will also be determined according to the ASTCT CRS Consensus Grading Scale.
Exploratory Objectives	**Corresponding Endpoints**
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

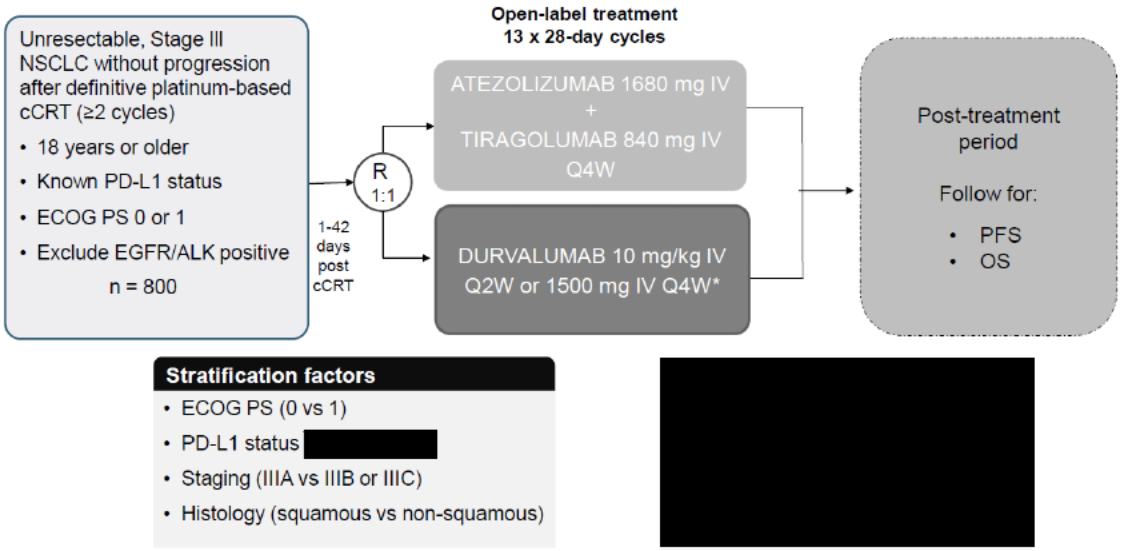
Exploratory Objectives	• Corresponding Endpoints
[redacted]	• [redacted] • [redacted]
[redacted]	• [redacted]

[redacted] ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; [redacted] 13; FAS = full analysis set; [redacted] IRF = Independent Review Facility; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PPAS = programmed death–ligand 1-positive analysis set; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; TTDM = time to distant metastasis; v = version

1.2 STUDY DESIGN

This is a Phase III, open-label, randomized, global, multicenter study designed to evaluate the efficacy and safety of atezolizumab in combination with tiragolumab compared with durvalumab administered to patients with locally advanced, unresectable Stage III NSCLC who have not progressed following concurrent platinum-based CRT as consolidation therapy. The study design is shown in Figure 1 :

Figure 1 Overview of Study Design



ALK = anaplastic lymphoma kinase (gene); cCRT = concurrent chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor (gene); iDMC = independent Data Monitoring Committee; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = Performance Status; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomization.

* For patients whose weight ≥ 30 kg.

[redacted]

This study will enroll approximately 800 patients. [redacted] Eligible patients will be randomized in a 1:1 ratio to receive either atezolizumab plus tiragolumab or durvalumab.

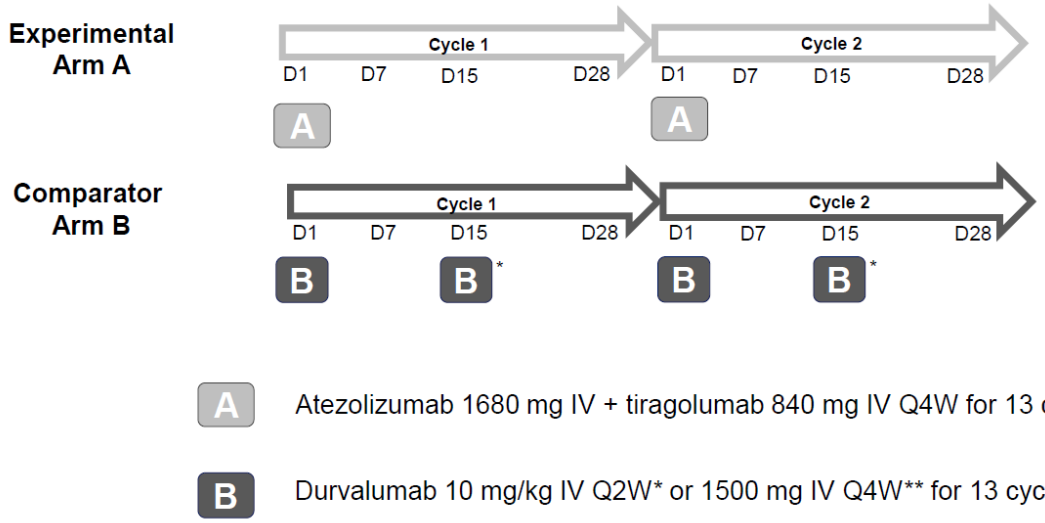
Eligible patients will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), PD-L1 expression, [redacted] tumor histology (non-squamous vs. squamous), and staging (Stage IIIA vs. Stage IIIB or IIIC).

In the experimental arm, atezolizumab will be administered to patients by intravenous (IV) infusion at a fixed dose of 1680 mg, followed by tiragolumab at a fixed dose of 840 mg administered by IV infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles (see Figure 2).

In the comparator arm, patients will receive durvalumab 10 mg/kg every 2 weeks (Q2W) administered by IV infusion on Days 1 and 15 of each 28-day cycle for a maximum of 13 cycles (not to exceed 26 doses) or fixed dose durvalumab at 1500 mg every 4 weeks

(Q4W) (for patients whose weight ≥ 30 kg), administered by IV infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles (see Figure 2). [redacted]

Figure 2 Dosing Schedule for Experimental and Comparator Arms



D = day; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks.
*On Day 15 of each 28-day cycle, patients in the comparator arm on Q2W durvalumab dosing will receive durvalumab 10 mg/kg IV.
**For patients whose weight ≥ 30 kg.

Treatment may be continued for 13 cycles, in the absence of metastatic disease, as long as patients are experiencing clinical benefit, as assessed by the investigator (INV), 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 will undergo tumor assessments at screening and every 8 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After completion of the Week 48 tumor assessment, tumor assessment will be required every 12 weeks (±7 days) regardless of treatment delays until confirmed, INV-assessed radiographic disease progression (as defined by growth of existing lesions, new lesions, or recurrence of previously resolved lesions) per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), withdrawal of consent, 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. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration, completion of study treatment) will continue scheduled tumor assessments at the frequency described

above until confirmed 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 confirmed by scan per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[redacted]

1.2.1 Treatment Assignment and Blinding

This is a Phase III, open-label, randomized study. After written informed consent has been obtained and eligibility has been established ([redacted]), the study site will obtain the patient's identification number and study treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomized to receive either tiragolumab plus atezolizumab or durvalumab. 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)
- PD-L1 expression, [redacted]
- Tumor histology of NSCLC (non-squamous vs. squamous)
- Staging (IIIA vs. IIIB or IIIC)

Staging will be performed according to the 8th revised edition of the American Joint Committee on Cancer (AJCC)/ Union Internationale Contre le Cancer (UICC) NSCLC staging system (Stage IIIA vs. Stage IIIB or IIIC).

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

1.2.2 Independent Review Facility

An Independent Review Facility (IRF) will be used to conduct a blinded radiology review of the imaging data and will provide an independent assessment of tumor response and progression for all patients according to a separate IRF Charter.

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) will be formed to evaluate safety during the study. [redacted]

[redacted]

The safety data will include patient disposition, demographic data, AEs (adverse events), and relevant laboratory data. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor, taking into consideration the iDMC's recommendation.

Members of the iDMC will be external to the Sponsor and will follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan.

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

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The primary objective of this study is to evaluate the efficacy of tiragolumab plus atezolizumab on IRF-assessed progression-free survival (IRF-PFS) in the programmed death-ligand 1-positive analysis set (PPAS) and Full Analysis Set (FAS) compared with durvalumab in patients with locally advanced unresectable Stage III non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation. A key secondary objective is to evaluate the efficacy of tiragolumab plus atezolizumab compared with durvalumab on the basis of OS in the PPAS and FAS.

The null (H_0) and alternative (H_1) hypotheses for the IRF-assessed PFS analysis and OS analysis can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in the tiragolumab plus atezolizumab arm and durvalumab arm, respectively:

$$H_0: S_A(t) = S_B(t) \text{ vs. } H_1: S_A(t) \neq S_B(t)$$

2.2 SAMPLE SIZE DETERMINATION

A total enrollment of approximately 800 patients is planned for this study [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.2 Primary Efficacy Endpoint: Independent Review Facility-Assessed Progression-Free Survival

The final analysis of the primary endpoint of IRF-assessed PFS will occur when approximately [redacted] PFS events have been observed in the PPAS, corresponding to a [redacted] Estimates of the number of events required to demonstrate efficacy in terms of IRF-assessed PFS are based on the following assumptions:

- 1:1 randomization ratio
- Survival curve follows the exponential distribution
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.2.3 Secondary Efficacy Endpoint: Overall Survival

The final analysis of the secondary endpoint of OS will occur when approximately [redacted] deaths have been observed in the PPAS and [redacted] deaths have been observed in the

FAS. Estimates of the number of events required to demonstrate efficacy in terms of OS are based on the following assumptions:

- 1:1 randomization ratio
- OS curve follows the exponential distribution
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

3. ANALYSIS SETS

The analysis sets are defined in Table 3 :

Table 3 Participant Analysis Sets

Participant Analysis Sets	Description
Full Analysis Set (FAS)	All randomized participants, regardless of whether or not the participant received the assigned treatment.
PD-L1 Positive Analysis Set (PPAS)	Participants in the FAS with PD-L1 positive [redacted].
Safety Analysis Set (SAS)	All randomized participants who received at least one dose of study treatment; participants will be included in the analyses according to the intervention they actually received.
PK Analysis Set	All participants who received at least one dose of study treatment and who have at least one post-baseline PK sample available.

Atezolizumab ADA Analysis Set	All participants who received at least one dose of atezolizumab treatment and with an ADA assay result from at least one post-baseline sample.
Tiragolumab ADA Analysis Set	All participants who received at least one dose of tiragolumab treatment and with an ADA assay result from at least one post-baseline sample.

ADA = anti-drug antibody; CDx = companion diagnostic; PK = pharmacokinetic; TC = tumor cell.

4. STATISTICAL ANALYSES

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

4.1 GENERAL CONSIDERATIONS

The efficacy analyses will be performed in the PPAS and FAS, with patients grouped according to the treatment assigned at randomization by IxRS.

Safety analyses will be performed in the Safety Analysis Set (SAS), with patients grouped according to the actual treatment received. Specifically, a patient will be included in the tiragolumab plus atezolizumab arm if the patient received any amount of tiragolumab or atezolizumab, including the case when tiragolumab or atezolizumab was received in error, regardless of the initial treatment assignment at randomization.

Hypothesis tests will be two-sided unless otherwise indicated. Baseline measurements are defined as the last available measurement obtained prior to the patient receiving the first dose of any component of study treatment, or prior to randomization for patients who were not treated, unless otherwise noted.

4.2 PRIMARY ENDPOINTS ANALYSIS

4.2.1 Definition of Primary Endpoints

The primary efficacy endpoints for this study are IRF-assessed PFS according to RECIST v1.1 in the PPAS and FAS. The corresponding estimands are defined in Table 1.

[redacted]

The primary efficacy endpoint is IRF-assessed PFS after randomization, defined as the time between the date of randomization and the date of first documented disease progression as assessed by the IRF according to RECIST v1.1, or death, whichever occurs first. Patients who have not experienced disease progression or died at the time

of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

4.2.2 Main Analytical Approach for Primary Endpoints

IRF-assessed PFS will be compared between treatment arms with use of the stratified log-rank test. The HR for IRF-assessed PFS will be estimated using a stratified Cox proportional hazards model. The 95% confidence interval (CI) for the HR will be provided. The stratification factors will be the same as the randomization stratification factors as entered in IxRS: ECOG Performance Status (0 vs. 1), PD-L1 status, [redacted] histology (squamous vs. non-squamous), and disease staging (Stage IIIA vs. Stage IIIB or Stage IIIC).

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

4.2.3 Sensitivity Analyses for Primary Endpoints

The following sensitivity analyses will be performed on IRF-assessed PFS in the PPAS and FAS to assess the robustness of the primary results.

[redacted]

- [redacted]

[redacted]

4.2.3.2 Stratification

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 IRF-assessed PFS will be compared using an unstratified log-rank test and the HR will be estimated from an unstratified Cox proportional hazards model.

4.2.4 Supplementary Analyses

The following supplementary analyses will be performed on IRF-assessed PFS in the PPAS and FAS to provide additional insights into the understanding of the treatment effect.

4.2.4.1 Subgroup Analyses for Primary Endpoints

The generalizability of IRF-assessed PFS results when comparing the tiragolumab plus atezolizumab arm to the durvalumab arm will be examined by estimating the treatment effect in [redacted]

[redacted]

4.3 SECONDARY ENDPOINTS ANALYSES

The secondary efficacy endpoints will be analyzed in the PPAS and the FAS, and the statistical testing of the hypotheses depends on the results of the primary endpoint analyses. The estimands for selected secondary endpoints are defined in Table 2.

4.3.1 Key Secondary Endpoints

4.3.1.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization.

OS will be analyzed through use of the same methods described for the IRF-assessed PFS analysis. [redacted] If IRF-assessed PFS is statistically significant in the PPAS but not in the FAS, OS in the PPAS will be assessed descriptively.

The details of analysis timing for OS are described in Section 4.7 .

4.3.1.2 Investigator-Assessed Progression-Free Survival

Investigator-assessed PFS is defined as the time between the date of randomization and the date of first documented disease progression, as assessed by the investigator according to RECIST v1.1, or death, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

INV-assessed PFS will be analyzed through use of the same methods described for the IRF-assessed PFS analysis.

4.3.1.3 Objective Response Rate

4.3.1.3.1 IRF-Assessed Objective Response Rate

A confirmed objective response is defined as either a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$ 4 weeks apart, as determined by the IRF according to RECIST v1.1. Patients who do not meet these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

Confirmed objective response rate (ORR) is defined as the proportion of patients who achieve a confirmed objective response. Confirmed ORR will be analyzed in the randomized patients with measurable disease at baseline.

An estimate of confirmed ORR and its 95% CI will be calculated using the Wilson score method for each treatment arm. CIs for the difference in confirmed ORRs between the two treatment arms will be determined using the Newcombe method. The confirmed ORR will be compared between the two treatment arms using the stratified Mantel-Haenszel test. The stratification factors of this analysis will be the same as those described in Section 4.2.2

4.3.1.3.2 Investigator-Assessed Objective Response

Confirmed ORR as determined by the INV according to RECIST v1.1 will also be analyzed. The analysis methods will be the same as those described for IRF-assessed ORR.

4.3.1.4 Duration of Response

4.3.1.4.1 IRF-Assessed Duration of Response

Duration of response (DOR) will be assessed in patients who achieved a confirmed objective response, as determined by the IRF according to RECIST v1.1. Duration of response 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 IRF 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 last tumor assessment date. Duration of response 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. Comparisons between treatment arms will be made for descriptive purposes.

Median DOR and corresponding 95% CIs will be estimated using Kaplan-Meier methodology for each treatment arm.

4.3.1.4.2 Investigator-Assessed Duration of Response

DOR for patients with confirmed objective response, as determined by the INV according to RECIST v1.1, will also be analyzed. The analysis methods will be the same as those described for IRF-assessed DOR.

4.3.1.5 Time to Confirmed Deterioration

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the European Organisation for Research and Treatment of Cancer (EORTC) scoring manual 3rd edition (Fayers et al. 2001). The QLQ-C30 and QLQ-LC13 are composed of both multi-item scales and single-item measures including emotional, functional scales, symptom scales, and a global health status/ quality of life (QoL) scale.

For multi-item scales, if >50% of items within the multi-item subscale are missing at a given timepoint, the multi-item score will be calculated on the basis of the non-missing items. If >50% of items are missing or if a single-item measure is missing, the subscale is missing. Otherwise, no imputation will be performed to replace missing scores. All EORTC scales and single-item measures will be linearly transformed so that each score has a range of 0-100. A high score for a functional/global health status scale represents a high or healthy level of functioning/health-related quality of life (HRQoL); however, a high score for a symptom scale or item represents a high level of symptomatology or problems.

Time to confirmed deterioration (TTCD) for each of the symptom scores including cough (Question 1, EORTC QLQ-LC13), shortness of breath (Questions 3-5, EORTC QLQ-LC13), Chest pain (Question 10, EORTC QLQ-LC13) and global health status (GHS) and physical functioning using the EORTC QLQ-C30, is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration on each respective score. Confirmed clinically meaningful deterioration in symptoms is defined as a clinically meaningful increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial clinically meaningful increase above baseline followed by death from disease within 60 days of initial deterioration. Confirmed clinically meaningful deterioration in GHS and physical functioning is defined as a clinically meaningful decrease from baseline in GHS or physical functioning scale score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death. A score change of ≥10 points is considered to be clinically meaningful by patients for lung cancer-related symptoms, GHS, and physical functioning subscale score (Osoba et al. 1998).

For TTCD, data for patients will be censored at the last time when they completed an assessment if they have not experienced a confirmed clinically meaningful deterioration event at the clinical cutoff date, or a clinically meaningful deterioration immediately followed by death due to progressive disease within 6 weeks. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. TTCD using the EORTC scale will be analyzed using the same methods as for PFS.

4.3.2 Sensitivity Analyses for Key Secondary Endpoints

4.3.2.1 Stratification

Sensitivity analyses of INV-assessed PFS and OS will be performed to assess the impact of stratification. The analyses will follow the same analysis methods as the primary endpoints with the exception that INV-assessed PFS and OS will be compared using an unstratified log-rank test and the HR will be estimated from the unstratified Cox proportional hazards model.

4.3.3 Supplementary Analyses for Key Secondary Endpoints

4.3.3.1 Subgroup Analysis for Secondary Endpoints

The generalizability of OS results when comparing the tiragolumab plus atezolizumab arm to the durvalumab arm will be examined by estimating the treatment effect in

[redacted]

4.3.3.2 Non-Protocol Anti-Cancer Therapy for Overall Survival

The impact of subsequent non-protocol anti-cancer therapy (NPT) on OS will be assessed depending on the number of patients who received NPT. If >10% of patients received NPT in either treatment arm, the discount method may be performed to compare treatment arms. The discount method uses a 'discounted' survival time after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. OS may be discounted according to a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g. 10%, 20%, 30%, etc.).

4.3.4 Supportive Secondary Endpoints

4.3.4.1 Progression-Free Survival Rate at Landmark Timepoints

The IRF-assessed PFS rate and investigator-assessed PFS rate at 12, 18 and 24 months after randomization will be estimated using Kaplan-Meier methodology for each treatment arm and the 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.

4.3.4.2 Overall Survival Rate at Landmark Timepoints

The OS rate at 12, 24, 36, 48 months will be estimated using Kaplan-Meier methodology for each treatment arm and the 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method, with standard errors computed using Greenwood's method.

4.3.4.3 Time to Death or Distant Metastasis

Time to death or distant metastasis (TTDM) is defined as the time between the date of randomization and the date of first documented distant metastasis as assessed by investigator according to RECIST v1.1, or death, whichever occurs first. Specifically, distant metastasis is defined as any new lesion that is outside of the radiation field. Patients who have not experienced distant metastasis nor died at the time of analysis

will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization. Comparisons between treatment arms will be made for descriptive purposes.

Kaplan-Meier methodology will be used to construct survival curves for each treatment arm and to estimate median TTDM for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median TTDM for each treatment arm (Brookmeyer and Crowley 1982). Additionally, the TTDM rate at selected time points at 12, 24, 36, 48 months will be provided.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

[redacted]

4.5 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the SAS (see Section 3), with patients grouped according to the actual treatment 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 or atezolizumab, regardless of the initial treatment assignment at randomization.

4.5.1 Extent of Exposure

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

4.5.2 Adverse Events

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Severity for all treatment-emergent AEs will be graded by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, and severity for cytokine release

syndrome (CRS) will also be graded by the investigator according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading scale.

All AEs will be summarized by treatment arm and NCI CTCAE grade. Cytokine-release syndrome will also be summarized by treatment arm and ASTCT consensus grade. In addition, common 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, adverse event of special interest (AESI) are identified by a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-Level Terms (HLTs), Preferred Terms (PTs) and Sponsor-defined custom events (CEs) from the AE clinical database by medical concept. Multiple occurrences of the same event will be counted once at the maximum severity.

For the safety analyses, “treatment-emergent” is defined as AEs 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 AEs up to the data cutoff date.

All deaths and causes of death will be summarized by treatment arm.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

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

4.5.3.2 Vital Signs

Vital signs outside normal limits among patients without abnormality at baseline will be summarized by treatment arm.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Study enrollment and reasons for discontinuation from the study will be summarized by treatment arm in the PPAS and FAS. Major protocol deviations, including major deviations with regards to the inclusion and exclusion criteria, will be summarized by treatment arm for the FAS. Study treatment disposition and reasons for study drug discontinuation will be summarized by treatment arm in the SAS.

4.6.2 Summaries of Treatment Group Comparability

Demographics (including age, sex, race) and baseline characteristics (e.g., PD-L1 expression, previous curative treatment, and ECOG Performance Status) will be

summarized overall and by treatment arm for both PPAS and FAS. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data, as appropriate.

4.6.3 Pharmacokinetic Analyses

Samples will be collected for pharmacokinetic (PK) analyses and to compare exposure in this study with that attained in previous studies. PK analyses will be conducted as appropriate based on the availability of data.

Serum concentrations of tiragolumab and atezolizumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and cycle, when appropriate and as data allow. Individual and median serum tiragolumab and atezolizumab concentrations will be plotted by treatment arm and day. Tiragolumab and atezolizumab concentration data may be pooled with data from other studies using an established population-PK model to derive PK parameters such as clearance, volume of distribution, and area under curve (AUC), as warranted by the data. Potential correlations of relevant PK parameters with safety, efficacy, or biomarker outcomes may be explored.

4.6.4 Immunogenicity Analyses

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

The number and proportion of treatment-emergent ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods for both tiragolumab and atezolizumab will be summarized by treatment arm.

[redacted]

[redacted]

5. SUPPORTING DOCUMENTATION

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

6. REFERENCES

Akazawa K, Nakamura T, and Palesch Y. Power of Logrank Test and Cox Regression Model in Clinical Trials with Heterogeneous Samples. Statistics in Medicine,1997;16:583-597.

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

DeMets D and Lan KKG. Interim analysis: the alpha spending function approach. Statistics in Medicine,1994;13:1341−52.

Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

Finkelstein DM. A proportional hazards model for interval-censored failure time data. Biometrics 1986:845-54

Friedman, M. Piecewise exponential models for survival data with covariates. Annals of Statistics 1982;10:101-13.

Lewis S and Clarke M. Forest plots: trying to see the wood and the trees. British Medical Journal, 2001;322:1479-80.

O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. Biometrics, 1979:549-56..

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. Journal of Clinical Oncology,1998;16:139−44.

Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21:2175-97.

Sun J. A non-parametric test for interval-censored failure time data with application to aids studies. Statistics in Medicine,1996;15:1387-1395.

Turnbull BW. Nonparametric estimation of a survivorship function with doubly censored data. Journal of the American Statistical Association 1974;69:169-73.

Signature Page for Statistical Analysis Plan SKY-03 RO7092284 - GO41854 - Publis
System identifier: RIM-CLIN-626778

Approval Task	[redacted] Company Signatory 07-Oct-2024 20:42:05 GMT+0000