

Official Title: A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study of Tiragolumab in Combination with Atezolizumab Plus Pemetrexed and Carboplatin/Cisplatin Versus Pembrolizumab Plus Pemetrexed and Carboplatin/Cisplatin in Patients with Previously Untreated Advanced Non-Squamous Non-Small-Cell Lung Cancer

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE II/III, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF TIRAGOLUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN VERSUS PEMBROLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NON SQUAMOUS NON-SMALL CELL LUNG CANCER

STUDY NUMBER: BO42592
STUDY NAME: SKYSCRAPER-06
VERSION NUMBER: 3
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Atezolizumab (RO5541267)
EUDRACT NUMBER: 2020-002851-39
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NCT NUMBER: NCT04619797
PLAN PREPARED BY: [REDACTED] Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

See electronic approval on the last page of this document

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

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, dated 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	24 February 2022	Version 4, 18 January 2022
2	11 May 2022	Version 4, 18 January 2022
3	see electronic date stamp on the last page of this document	Version 4, 18 January 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ASTCT	American Society for Transplantation and Cellular Therapy
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
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
FAS	full analysis set
GHS	global health status
HR	hazard ratio
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IL46	Item List 46
IRF	Independent Review Facility
IxRS	interactive voice/web-based response system
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
Pbo+Pembro+Chemo	placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin
PD-L1	programmed death ligand 1
PF	physical functioning
PFS	progression-free survival
PR	partial response

PK	pharmacokinetic
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
QOL	quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	Statistical Analysis Plan
TC	tumor cell
Tira+Atezo+Chemo	tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin
TPS	tumor proportion score
TTCD	time to confirmed deterioration

1. **INTRODUCTION**

Study BO42592 (SKYSCRAPER-06) is a Phase II/III, randomized, double-blind, placebo-controlled study of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin versus pembrolizumab plus pemetrexed and carboplatin/cisplatin in patients with previously untreated advanced non-squamous non-small cell lung cancer (NSCLC). The background of the study can be found in the study protocol.

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for SKYSCRAPER-06 after the study continues into a Phase III study following an interim efficacy analysis reviewed by the independent Data Monitoring Committee (iDMC).

1.1 **OBJECTIVES, ENDPOINTS, AND ESTIMANDS**

All objectives and corresponding endpoints for the expanded Phase III study are outlined in [Table 1](#) below. The two treatment arms under consideration are tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (hereinafter referred to as Tira+Atezo+Chemo) and placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin (herein after referred to as Pbo+Pembro+Chemo).

The term "study treatment" refers to all protocol-mandated treatments assigned to patients as part of this study and includes tiragolumab/placebo, atezolizumab, pembrolizumab, pemetrexed and carboplatin/cisplatin during the induction phase; tiragolumab/placebo, atezolizumab, pembrolizumab and pemetrexed during the maintenance phase.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
<ul style="list-style-type: none">To evaluate the efficacy of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo	<ul style="list-style-type: none">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 firstOS: defined as the time from randomization to death from any cause

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Objectives	Corresponding Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo 	<ul style="list-style-type: none"> IRF-PFS, defined as the time from randomization to the first occurrence of disease progression as determined by an IRF according to RECIST v1.1, or death from any cause, whichever occurs first The PFS and OS in patients with PD-L1 expression at TC\geq50% and TC\geq1% cutoff, as determined by central testing with Ventana PD-L1 (SP263) assay PFS rate at 6 months and 12 months, 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, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR on two consecutive occasions \geq4 weeks apart), as determined by the investigator according to RECIST v1.1 in patients with measurable disease at baseline DOR for 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 TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30, and in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
<ul style="list-style-type: none"> To evaluate the safety of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo 	<ul style="list-style-type: none"> Incidence and severity of adverse events, with severity determined according to NCI CTCAE, v 5.0 <ul style="list-style-type: none"> [REDACTED]
<ul style="list-style-type: none"> To characterize the tiragolumab and atezolizumab pharmacokinetics (PK) profile 	<ul style="list-style-type: none"> Serum concentrations of tiragolumab and atezolizumab at specified timepoints
<ul style="list-style-type: none"> To evaluate the immune response to tiragolumab and atezolizumab 	<ul style="list-style-type: none"> 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

Table 1 Objectives and Corresponding Endpoints (cont.)

ADA=anti-drug antibody; ASTCT=American Society for Transplantation and Cellular Therapy; CR=complete response; CRS=cytokine release syndrome; 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; HRQoL=health-related quality of life; IL46=Item List 46; IRF=independent review facility; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; Pbo+Pembro+Chemo=placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin; PD-L1=programmed death ligand 1; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; PRO=patient-reported outcome; QLQ-C30=Quality-of-Life Questionnaire Core 30; QLQ-LC13=Quality of Life Questionnaire-Lung Cancer 13; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors; TC=tumor cell; Tira+Atezo+Chemo=tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin; 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 Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

Table 2 Objectives and Estimands

Primary Objective	Estimand Definition
<ul style="list-style-type: none"> To evaluate the efficacy of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo 	<ul style="list-style-type: none"> <u>Population</u>: 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). <u>Treatments</u>: <ul style="list-style-type: none"> Experimental: tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (induction phase; four 21-day cycles) followed by tiragolumab in combination with atezolizumab and pemetrexed (maintenance phase; 21-day cycles) Control: placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (induction phase; four 21-day cycles) followed by placebo in combination with pembrolizumab and pemetrexed (maintenance phase; 21-day cycles)

Table 2 Objectives and Estimands (cont.)

Primary Objective (cont.)	Estimand Definition (cont.)
	<ul style="list-style-type: none"> • <u>Intercurrent events</u>: <ul style="list-style-type: none"> ○ Start of non-protocol anti-cancer therapy (NPT) prior to the respective event of interest ○ Early discontinuation from study treatment for any reason prior to the respective event of interest • <u>Handling of intercurrent events</u>: A treatment-policy with regards to the intercurrent events listed above will be applied for the primary analysis • <u>Summary measure</u>: Hazard ratio for the respective variable
Selected Secondary Objectives	Estimand Definition
<ul style="list-style-type: none"> • To evaluate the efficacy of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo 	<p>The estimand for secondary endpoint of confirmed ORR is defined similarly as for the primary endpoints in terms of population and treatments; the other attributes are defined as follows:</p> <ul style="list-style-type: none"> • <u>Variable</u>: Whether participants 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 • <u>Intercurrent events</u>: <ul style="list-style-type: none"> ○ 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 • <u>Handling of intercurrent events</u>: A treatment-policy with regards to the intercurrent events listed above will be applied for the analysis • <u>Summary measure</u>: difference in proportions

Table 2 Objectives and Estimands (cont.)

Selected Secondary Objectives (cont.)	Estimand Definition (cont.)
<ul style="list-style-type: none"> To evaluate the quality of life of patients treated with Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo 	<p>The estimand for 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:</p> <ul style="list-style-type: none"> <u>Variable</u>: Time from randomization until the first confirmed clinically meaningful deterioration on physical functioning and GHS/QoL as measured by the EORTC QLQ-C30 or in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13; confirmed clinically meaningful deterioration is defined as a clinically meaningful change from baseline that must be held for at least two consecutive assessments or an initial clinically meaningful change from baseline followed by death from any cause within 3 weeks. <u>Intercurrent events</u>: <ul style="list-style-type: none"> 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 <u>Handling of intercurrent events</u>: 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. <u>Summary measure</u>: Hazard Ratio for TTCD

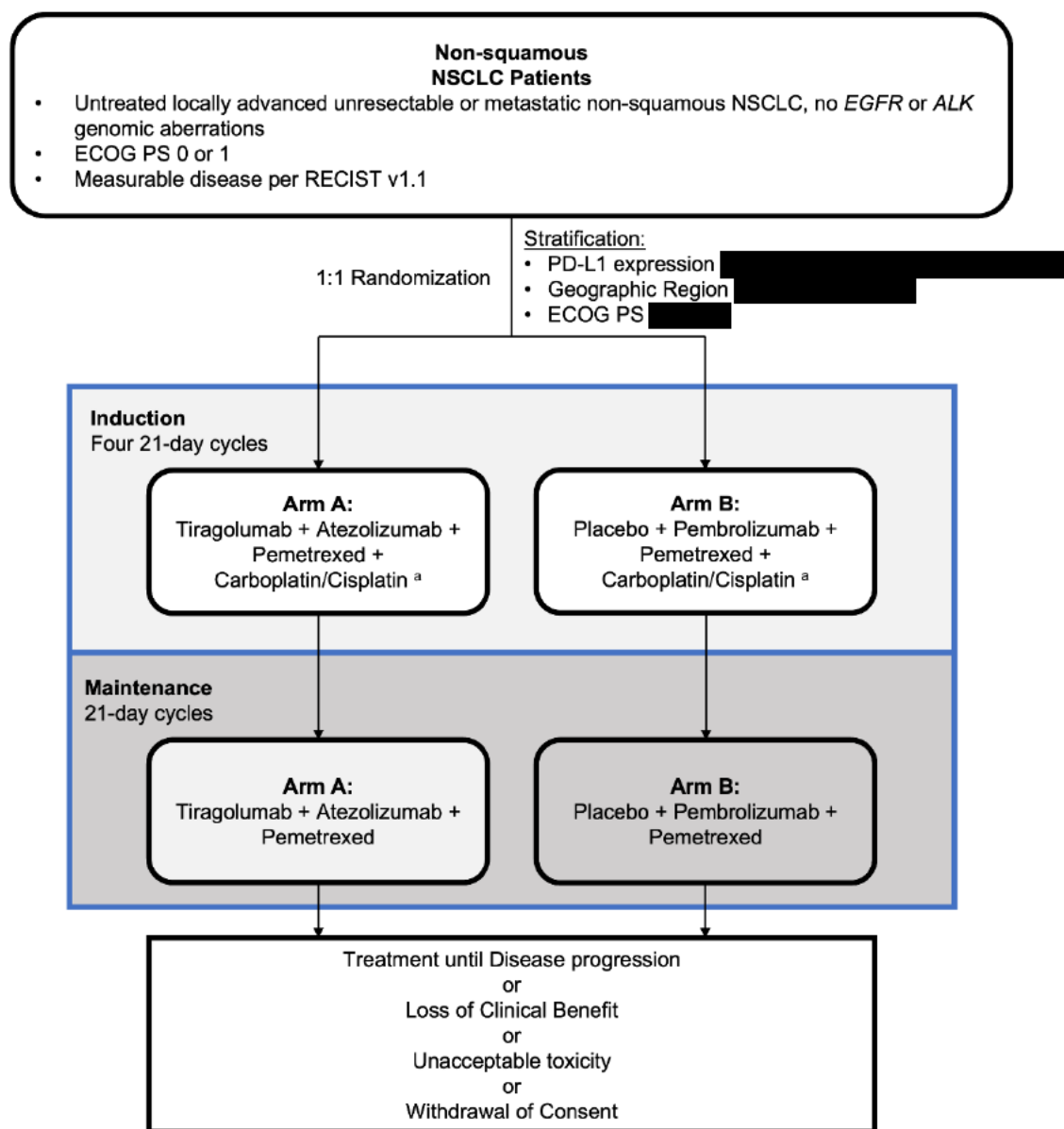
CR=complete response; EORTC=European Organization for Research and Treatment of Cancer; GHS=global health status; NSCLC=non-small cell lung cancer; NPT=non-protocol anti-cancer therapy; Pbo+Pembro+Chemo=placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin; PR=partial response; QLQ-C30=Quality-of-Life Questionnaire Core 30; QLQ-LC13=Quality-of-Life Questionnaire–Lung Cancer 13; QoL=Quality of Life; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; Tira+Atezo+Chemo=tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin; TTCD=time to confirmed deterioration.

1.2 STUDY DESIGN

This is a randomized, Phase II/III, global, multicenter, double-blind study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC.

The study schema is shown in [Figure 1](#).

Figure 1 Study Schema



ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; ECOG PS=Eastern Cooperative Oncology Group Performance Status; iDMC=independent Data Monitoring Committee; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand 1; RECIST (v1.1)=Response Evaluation Criteria in Solid Tumors, Version 1.1; TC=tumor cells; TPS=tumor proportion score.

^a Safety and tolerability data will be assessed by an independent Data Monitoring Committee approximately 6 months from randomization of the first patient.

^b If treatment continued beyond disease progression.

Approximately [REDACTED] patients will be enrolled in the Phase II part of the study. [REDACTED]

[REDACTED]

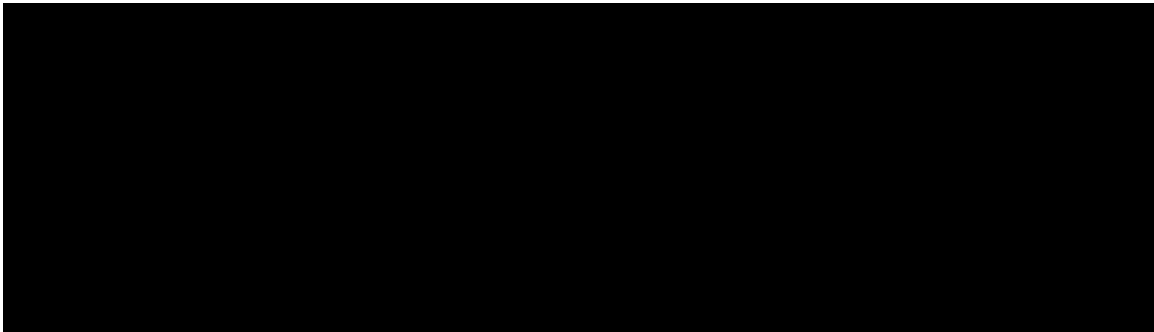
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[REDACTED]

Induction treatment with tiragolumab in combination with atezolizumab plus pemetrexed and cisplatin/carboplatin or placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin will be administered on a 21-day cycle for 4 cycles.

Following the induction phase, patients will continue maintenance therapy with either tiragolumab in combination with atezolizumab and pemetrexed or placebo in combination with pembrolizumab and pemetrexed.

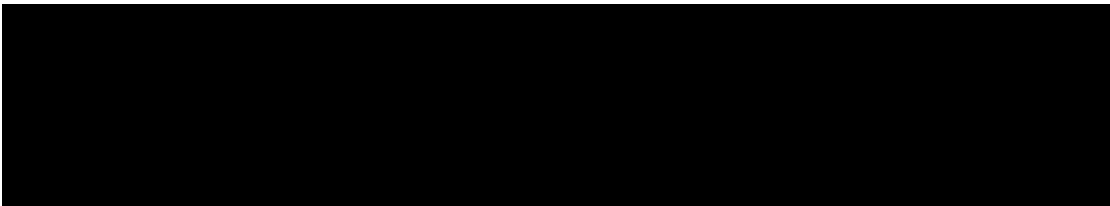
[REDACTED]



1.2.1 Treatment Assignment and Blinding

During both the Phase II part and Phase III expansion of the study, eligible patients will be randomized 1:1 to receive Tira+Atezo+Chemo or Pbo+Pembro+Chemo. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the following stratification factors:

- Programmed death ligand 1 (PD-L1) expression [REDACTED]
- Geographic region [REDACTED]
- Eastern Cooperative Oncology Group (ECOG) Performance Status [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 IRF will be conducted for the expanded Phase III study.

1.2.3 Data Monitoring

An iDMC will be formed to evaluate safety at regular intervals during the study and to conduct the interim efficacy analysis. Sponsor will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC's roles and responsibilities.

[REDACTED]

[REDACTED]

[REDACTED]

2. STATISTICAL HYPOTHESES

The purpose of the Phase III study is hypothesis testing and estimation regarding the effect of Tira+Atezo+Chemo on progression-free survival (PFS) and/or overall survival (OS) compared with Pbo+Pembro+Chemo. The primary objective of this study is to evaluate the efficacy of Tira+Atezo+Chemo compared with Pbo+Pembro+Chemo in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC.

[REDACTED]

[REDACTED]

3. SAMPLE SIZE DETERMINATION

Approximately [REDACTED] patients in total may be randomized in a 1:1 ratio into the expanded Phase III study. This comprises patients randomized into the Phase II part (referred to as the Phase II cohort) and additional patients randomized in the Phase III expansion (referred to as the Phase III expansion cohort).

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.2 CO-PRIMARY ENDPOINT: PFS

The primary analysis of the co-primary endpoint of PFS will occur [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. ANALYSIS SETS

The following analysis sets are defined in [Table 4](#).

Table 4 Analysis Sets

Analysis set	Definition
Full analysis set (FAS)	All patients randomized to the expanded Phase III study, including the Phase II cohort and the Phase III expansion cohort, whether or not the patients received the assigned treatment.
Safety-evaluable set	All patients randomized to the expanded Phase III study who received at least one dose of study treatment.
Pharmacokinetic-evaluable set	All participants who received any dose of atezolizumab or tiragolumab 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
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

ADA=anti-drug antibody; PK=pharmacokinetic.

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 CONSIDERATION

All efficacy analyses will be performed in full analysis set (FAS), unless otherwise specified. Patients will be analyzed according to the treatment assigned at randomization by IxRS for the efficacy analyses, regardless of whether they receive any assigned study drug.

All safety analyses will be performed in the safety-evaluable set, unless otherwise specified. Participants will be analyzed according to the treatment they actually received for the safety analyses. Specifically, a patient will be included in the Tira+Atezo+Chemo Arm in the safety analyses if the patient receives any amount of tiragolumab or atezolizumab, 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 PARTICIPANT 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 ENDPOINT ANALYSIS

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

5.3.1 Definition of Primary Endpoints

5.3.1.1 Progression-Free Survival

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

- Population: Patients with previously untreated locally advanced unresectable or metastatic non-squamous NSCLC.
- Variable: 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.
- Treatments:
 - Experimental: tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (induction phase; four 21-day cycles) followed by tiragolumab in combination with atezolizumab and pemetrexed (maintenance phase; 21-day cycles)
 - Control: placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (induction phase; four 21-day cycles) followed by placebo in combination with pembrolizumab and pemetrexed (maintenance phase; 21-day cycles)
- Intercurrent events:
 - Start of NPT prior to a PFS event
 - Early discontinuation from study treatment for any reason prior to a PFS event
- Handling of intercurrent events: A treatment-policy with regards to the intercurrent events listed above will be applied for the primary analysis
- Summary measure: HR for PFS

Patients who have not experienced disease progression or have not died at the time of each planned 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: Patients with previously untreated locally advanced unresectable or metastatic non-squamous NSCLC.

- Variable: Time from randomization to death
- Treatments:
 - Experimental: tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (induction phase; four 21-day cycles) followed by tiragolumab in combination with atezolizumab and pemetrexed (maintenance phase; 21-day cycles)
 - Control: placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (induction phase; four 21-day cycles) followed by placebo in combination with pembrolizumab and pemetrexed (maintenance phase; 21-day cycles)
- Intercurrent events:
 - Start of NPT
 - Early discontinuation from study treatment for any reason
- Handling of intercurrent events: A treatment-policy with regards to the intercurrent events listed above will be applied for the primary analysis
- Summary measure: Hazard ratio for OS

Participants who are not reported as having died by the data cutoff date will be censored at the date when they were last known to be alive. Participants with no postbaseline information will be censored at the date of randomization.

5.3.2 Main Analytical Approach for Primary Endpoints

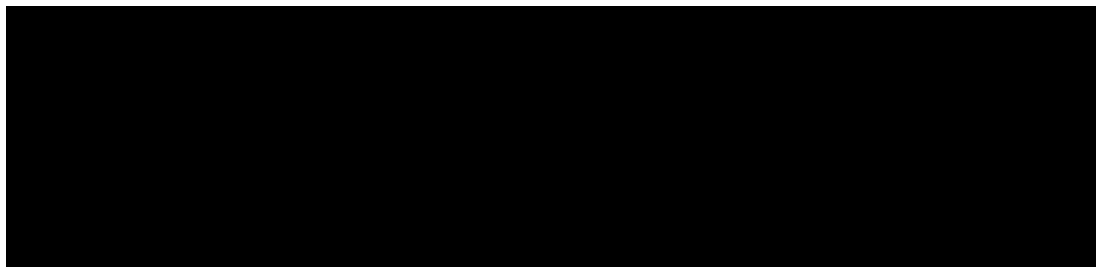
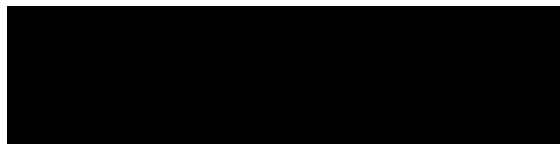
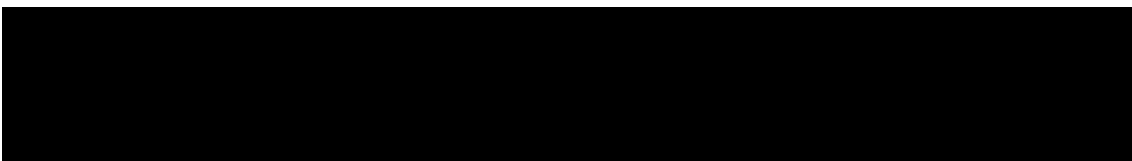
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



The weights w_f , w_2 , w_3 are determined prior to the interim efficacy analysis (see Section 5.8.1.1) and are based on the projected number of events at the time of the analyses. Let Δ_f , Δ_2 , Δ_3 denote the total number events expected at the time of the interim efficacy analysis during the Phase II part of the study, cumulative number of events for the Phase II cohort at the analyses specified for the Phase III, and cumulative number of events in the Phase III expansion cohort at the analyses specified for the Phase III, respectively, the weights can be expressed as follows:

$$w_f = \sqrt{\frac{\Delta_f}{\Delta_2 + \Delta_3}}$$

$$w_2 = \sqrt{\frac{\Delta_2 - \Delta_f}{\Delta_2 + \Delta_3}}$$

$$w_3 = \sqrt{\frac{\Delta_3}{\Delta_2 + \Delta_3}}$$

Two-sided p-value based on $z_{p2/3}$ will be compared to two-sided type I error, 0.004, allocated for PFS testing for the PFS primary analysis. Based on the assumptions listed in Section 3.2, the values to be used for the PFS primary analysis are summarized in the Table 5 below.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] will be calculated at the time of analysis based on the actual number of events observed in the FAS (see Section 5.8.1.2). The actual p-value boundaries will be calculated from multivariate normal distribution taken into consideration of the covariance matrix of $z_{P2/3}$ as described in Section 6, Appendix 1.

[REDACTED]

[REDACTED] 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

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 to evaluate the treatment benefit in which patients in either treatment arm 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 Primary Endpoints

Sensitivity analyses of the primary endpoints will be performed to assess the impact of stratification. These analyses will follow the same analyses methods as the primary endpoints with the exception that the HR will be estimated from unstratified Cox proportional hazards model (see also Section [5.3.2](#)).

Additional sensitivity analyses may be considered if appropriate.

5.3.5 Supplementary Analyses for Primary Endpoints

The following supplementary analyses use a different handling rule of intercurrent events for the primary efficacy endpoints 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

[REDACTED]

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

[REDACTED]

5.3.5.1 Subgroup Analyses for Primary Endpoints

The generalizability of OS and PFS results when comparing the Tira+Atezo+Chemo arm to the Pbo+Pembro+Chemo arm will be investigated by estimating the treatment effect in subgroups defined by demographics (e.g., age, sex, race/ethnicity, geographic region [REDACTED]), baseline prognostic characteristics (e.g., ECOG Performance Status and smoking status). [REDACTED]

(see Section 5.8.1.1).

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 assessed by Independent Review Facility

The estimand of IRF-PFS is defined similarly as for the co-primary endpoints of PFS and OS in Section 5.3.1 with the exception of the following:

- Variable: the time from randomization to the first occurrence of disease progression as determined by an IRF according to RECIST v1.1, or death from any cause, whichever occurs first
- Intercurrent events:
 - Start of NPT prior to an IRF-PFS event
 - Early discontinuation from study treatment for any reason prior to an IRF-PFS event

Same estimation approaches for investigator-assessed PFS specified in Section 5.3 will be used to analyze IRF-PFS.

5.4.1.2 Progression-Free Survival and Overall Survival for the SP263 PD-L1 Subpopulation

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

- Population: Participants with previously untreated locally advanced unresectable or metastatic non-squamous NSCLC and PD-L1 expression at TPS/TC < 1%, 1%–49%, or ≥ 50% cutoff determined by central testing using the investigational VENTANA SP263 CDx assay.

Same estimation approaches for PFS and OS specified in Section 5.3 will be applied, with the exception that the stratification factors used for the stratified analyses will be geographic region [REDACTED] and ECOG Performance Status [REDACTED]

5.4.1.3 Confirmed Objective Response Rate

Confirmed objective response rate (ORR) is defined as the proportion of participants with a confirmed objective response (i.e., complete response [CR] or partial response [PR] on two consecutive occasions ≥ 4 weeks apart), as determined by the investigator according to RECIST v1.1.

The estimand for the key secondary endpoint is defined as follows:

- Population: Participants with previously untreated locally advanced unresectable or metastatic non-squamous NSCLC
- Variable: whether participants 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
- Treatments:
 - Experimental: tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (induction phase; four 21-day cycles) followed by tiragolumab in combination with atezolizumab and pemetrexed (maintenance phase; 21-day cycles)
 - Control: placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (induction phase; four 21-day cycles) followed by placebo in combination with pembrolizumab and pemetrexed (maintenance phase; 21-day cycles)
- 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: A treatment-policy with regards to the intercurrent events listed above will be applied for the analysis
- Summary measure: difference in proportions

The analysis set for confirmed ORR will be FAS with measurable disease at baseline. Confirmed ORR will be 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 Progression-Free Survival Rate at Specific Timepoints

The PFS rate at 6 months and 12 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 PFS rates

between the two treatment arms will be estimated using the normal approximation method.

5.4.2.2 Overall Survival Rate at Specific Timepoints

The OS rate at 12 months and 24 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.

5.4.2.3 Duration of Response

Duration of response (DOR) will be assessed in a non-randomized subset of patients, specifically, patients who had measurable disease at baseline and 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. Median DOR and corresponding 95% CIs will be estimated using Kaplan-Meier methodology for each treatment arm.

5.4.2.4 Time to Confirmed Deterioration

Patient-reported lung cancer related symptoms, cough, dyspnea and chest pain are collected and measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). A lower score for each of the individual symptoms represents (or indicates) a lower level of patient-reported symptom burden. 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 EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30). A higher score for the physical function subscale represents a higher/healthier level of functioning and a higher score for the GHS/QoL subscale represents a higher health-related QoL.

All scales will be linearly transformed so that each score will range from 0 to 100. A score increase of at least 10 points in lung-cancer related symptoms and a score decrease of at least 10 points in GHS/QoL and PF scale score is perceived as [REDACTED]

[REDACTED] ([Osoba et al. 1998](#)).

The estimand for time to confirmed deterioration (TTCD) is defined as the follows:

- Population: Patients with previously untreated locally advanced unresectable or metastatic non-squamous NSCLC
- Variable: Time to confirmed deterioration for cough, dyspnea, and chest pain symptoms with use of the EORTC QLQ-LC13, GHS/QoL and PF with use of the EORTC QLQ-C30 is defined as the time from the date of randomization until the first

confirmed

- Treatments:
 - Experimental: tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (induction phase; four 21-day cycles) followed by tiragolumab in combination with atezolizumab and pemetrexed (maintenance phase; 21-day cycles)
 - Control: placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (induction phase; four 21-day cycles) followed by placebo in combination with pembrolizumab and pemetrexed (maintenance phase; 21-day cycles)
- Intercurrent events:
 - Start of NPT prior to a confirmed clinical meaningful deterioration
 - Early discontinuation from study treatment for any reason prior to a confirmed clinical 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: Hazard Ratio 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 died before reporting any clinical meaningful deterioration will be censored at the last time when they completed an assessment. TTCD will be analyzed using the same estimation methods as for PFS.

5.5 EXPLORATORY ENDPOINTS ANALYSIS

5.5.1 Patient-Reported Outcomes

Completion/compliance rates will be summarized at each visit by the treatment arm for all of the items and subscales of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires, and EORTC Item List 46 (IL46) (an item for trouble with side effects). Completion rates will be summarized by the number and the proportion of patients who completed the patient-reported outcome (PRO) questionnaires among those expected to

complete the questionnaires at each visit. Reasons for non-completion will also be summarized if available.

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires according to the EORTC scoring manual guidelines. The analyses will be performed on the FAS for EORTC QLQ-C30 and EORTC QLQ-LC13.

EORTC IL46 will be primarily descriptive (frequency counts and percentages). The IL46 assesses bother with the side effects of treatment and will be analyzed at the item level. The change in the frequency of response from baseline in IL46 will be summarized at each visit by treatment arm. The analyses of EORTC IL46 will be performed on the safety evaluable set. Results from these exploratory analyses will be presented separately from the other safety analyses.



5.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the safety-evaluable set (see Section 4), with participants grouped according to whether any tiragolumab or atezolizumab treatment was received (i.e., participants who received any dose of tiragolumab or atezolizumab will be included in the Tira+Atezo+Chemo arm).

5.6.1 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.

5.6.2 Adverse Events

Safety endpoints will include the incidence and severity of AEs, including serious adverse events (SAEs) and adverse events of special interest (AESI), and clinical laboratory results following the administration of study drugs. Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (and also according to the American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading scale for cytokine release syndrome [CRS]). All AEs will be summarized by treatment arm and NCI CTCAE grade and also ASTCT consensus grade for CRS. In addition,

SAEs and AEs leading to study treatment discontinuation, dose interruption or modification will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

In addition, common AEs, treatment-related AEs, SAEs, AEs leading to study treatment discontinuation, dose interruption or modification, Grade 3-4 AEs, and fatal AEs (Grade 5) will be summarized accordingly. For the purpose of analyses, AEs are identified by a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-Level Terms (HLTs), Preferred Terms (PTs) and Sponsor-defined adverse event grouped terms (AEGTs) from the AE clinical database by medical concept. The AEs will be summarized by treatment arm and CTCAE grade.

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

Key AEs that occurred during the induction and maintenance therapy phases may also be summarized separately.

Listings of AEs will include all treatment-emergent AEs up to the data cutoff date. Deaths during the study treatment period and those reported during the follow-up period after treatment completion or discontinuation and causes of death will be summarized by treatment arm.

5.6.3 Laboratory Data

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

5.6.4 Vital Signs

Vital signs will be summarized by treatment arm.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

Study enrollment, major protocol deviations will be summarized by treatment arm for the FAS.

5.7.2 Summaries of Treatment Group Comparability

Demographic characteristics (age, sex, race/ethnicity), baseline prognostic characteristics (e.g., smoking status) and stratification factors (ECOG Performance Status, PD-L1 expression [REDACTED] Geographic region [REDACTED]) will be summarized by treatment arm for the FAS.

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 number and proportion of tiragolumab and atezolizumab treatment-emergent anti-drug antibody (ADA)-positive patients and ADA-negative patients will be summarized.

[REDACTED]

The immunogenicity analyses will include patients with any tiragolumab and/or atezolizumab ADA assessments, with patients grouped according to the treatment received.

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. **SUPPORTING DOCUMENTATION**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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