PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB COMPARED WITH PLACEBO PLUS ATEZOLIZUMAB IN PARTICIPANTS WITH COMPLETELY RESECTED STAGE IIB, IIIA, OR SELECT IIIB, PD-L1 POSITIVE, NON–SMALL CELL LUNG CANCER WHO HAVE RECEIVED ADJUVANT PLATINUM-BASED CHEMOTHERAPY**
PROTOCOL NUMBER:	GO45006
STUDY NAME:	SKYSCRAPER-15
VERSION NUMBER:	1
TEST PRODUCT(S):	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 129258 EU CT Number: 2023-506696-10-00 PS ID: To be determined CIV ID: To be determined NCT Number: To be determined
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB COMPARED WITH PLACEBO PLUS ATEZOLIZUMAB IN PARTICIPANTS WITH COMPLETELY RESECTED STAGE IIB, IIIA, OR SELECT IIIB, PD-L1 POSITIVE, NON–SMALL CELL LUNG CANCER WHO HAVE RECEIVED ADJUVANT PLATINUM-BASED CHEMOTHERAPY**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or its designee.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB COMPARED WITH PLACEBO PLUS ATEZOLIZUMAB IN PARTICIPANTS WITH COMPLETELY RESECTED STAGE IIB, IIIA, OR SELECT IIIB, PD-L1 POSITIVE, NON–SMALL CELL LUNG CANCER WHO HAVE RECEIVED ADJUVANT PLATINUM-BASED CHEMOTHERAPY**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 129258 EU CT Number: 2023-506696-10-00 PS ID: To be determined CIV ID: To be determined NCT Number: To be determined

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered to participants with PD-L1 positive (≥1% tumor cells [TC] by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA and select IIIB (T3N2) non–small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in the PD-L1≥ 50% TC and PD-L1≥% TC populations	• Disease-Free Survival, as assessed by investigator, in the PD-L1≥ 50% TC population. The estimand for investigator-assessed DFS is defined as follows: – Population: Participants with completely resected tumors with PD-L1 high (≥50% TC by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA, or select IIIB NSCLC who have received adjuvant chemotherapy – Variable: Time from randomization to the occurrence of local/regional or distant recurrence of NSCLC, new primary NSCLC, or death from any cause (whichever occurs first), as determined by the investigator – Treatment: ▪ Tiragolumab plus atezolizumab: tiragolumab 840 mg plus atezolizumab 1680 mg administered by IV co-infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles, approximately 1 year

Objectives and Endpoints (cont).

Primary Objective (cont.)	Corresponding Endpoint (cont.)
	▪ Placebo plus atezolizumab: placebo plus atezolizumab 1680 mg administered by IV co-infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles, approximately 1 year – Intercurrent events: ▪ Early discontinuation from study treatment for any reason: a treatment policy strategy will be used ▪ Start of non-protocol anti-cancer therapy prior to the respective event of interest: a treatment policy strategy will be used – Population-level summary: Hazard ratio for DFS – DFS, as assessed by investigator, in the PD-L1 ≥ 1% TC population. The estimand is defined the same way as for investigator-assessed DFS in the PD-L1 ≥ 50% TC population, except for the following:Population: Participants with completely resected PD-L1 positive (≥ 1% TC by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA, or select IIIB NSCLC who have received adjuvant chemotherapy
Secondary Objectives	Corresponding Endpoints
• To 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 v5.0
• To evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Overall Survival • 3-year, 5-year, and 7-year DFS rates
• To evaluate the health-related quality of life of participants treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Health-related quality of life on the basis of proportion of participants who maintain or meaningfully improve from baseline in patient-reported role, emotional, and physical functioning and GHS/QOL over the course of treatment

Objectives and Endpoints (cont).

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
• To characterize the PK of tiragolumab plus atezolizumab	• Serum concentration of tiragolumab at specified timepoints • Serum concentration of atezolizumab at specified timepoints
• To evaluate the immune response to tiragolumab and 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

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, randomized, double-blind, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered in participants with PD-L1 ≥ 1% TC Stage IIB, IIIA, or select IIIB (T3N2 only) NSCLC following resection and adjuvant platinum-based chemotherapy.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult population
Control Method:	Placebo	**Population Diagnosis or Condition:**	Participants with PD-L1 ≥1% TC Stage IIB, IIIA, or select IIIB (T3N2 only) NSCLC following resection and adjuvant platinum-based chemotherapy.
Interventional Model:	Parallel group	**Population Age:**	≥18 years
Test Product{s}:	Tiragolumab Atezolizumab	**Site Distribution:**	Multi-site
Active Comparator:	Placebo Atezolizumab	**Study Intervention Assignment Method:**	Randomizatio
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 1150

STUDY TREATMENT

Tiragolumab or placebo will be administered as 600 mg/10 mL, 840 mg Q4W, IV infusion.

Atezolizumab will be administered as 1200 mg/20 mL or 840 mg/14 mL, 1680 mg Q4W, IV infusion.

The following dosing regimen is recommended for tiragolumab when administered in combination with atezolizumab:.

- Tiragolumab 840 mg co-infused with atezolizumab 1680 mg every four weeks (Q4W)

In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., atezolizumab plus tiragolumab).

Modification of the tiragolumab/placebo and atezolizumab dose is not permitted in this study.

DURATION OF PARTICIPATION

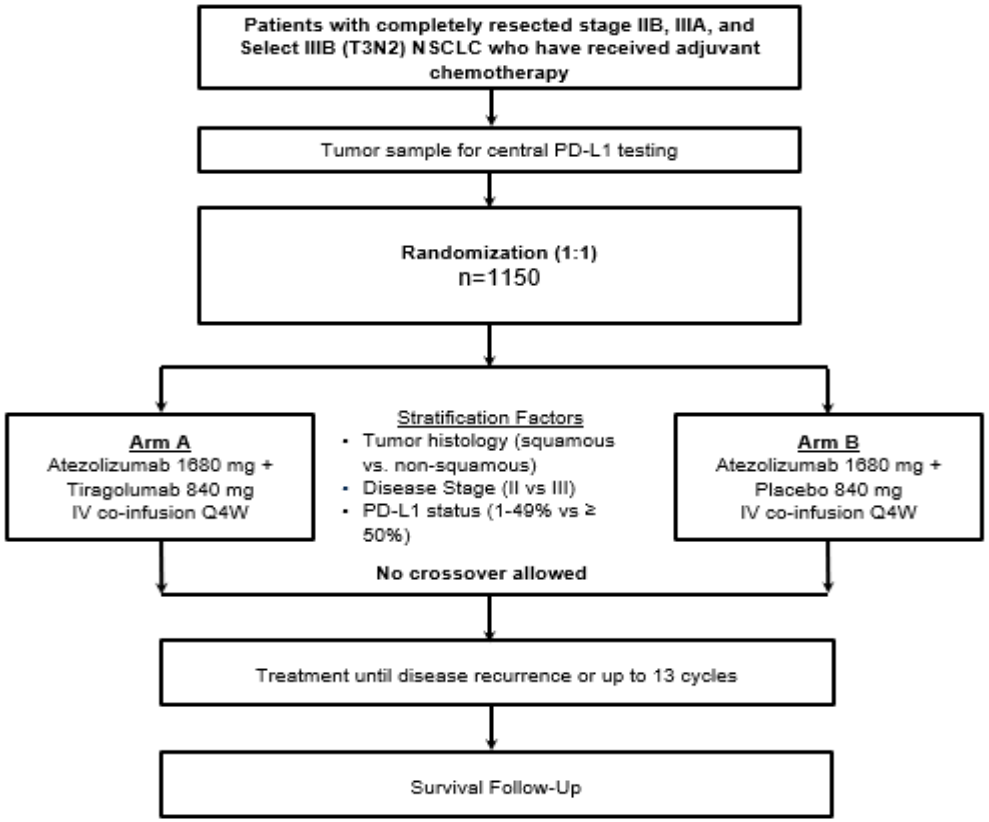
Treatment will continue until withdrawal or death due to any cause.

COMMITTEES

Independent Committees:	independent Data Monitoring Committee (iDMC)
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Schema



NSCLC = non small cell lung cancer; Q4W = every 4 weeks.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
Signed ICF(s) [d] - main ICF signing may occur up to 60 days prior to randomization	Section 8 and A1–3	x				
Tumor tissue specimen or slides for central PD-L1 testing and exploratory biomarkers [e]	Section 8.7	x				
EGFR and *ALK* mutational status (if applicable)	Section 4.1	x				
Demographics	Section 8	x				
Medical history	Section 8	x				
HIV, HBV, HCV, and EBV serology	Appendix 2	x				
HIV and HCV RNA	Appendix 2	If applicable				
CD4+ T-cell count	Appendix 2	If applicable				

Table 1 Schedule of Activities (cont.)

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
HBV DNA [f]	Appendix 2	If applicable		If applicable	If applicable	
EBV DNA	Appendix 2	If applicable				
Urinalysis (dipstick permitted) (specific gravity, pH, glucose, protein, ketones, and blood)	Appendix 2	x		as clinically indicated	Serum or urine test (if positive, serum test required to confirm)	
Pregnancy test (women of childbearing potential only) [g, h]	Section 8.2.5 and Appendix 2		Serum test required	Serum or urine test (if positive, serum test required to confirm)		
ECG	Section 8.2.3	x		as clinically indicated		
Concomitant medications	Section 6.8	x		x	x	
ECOG Performance Status [h]	Section 4.1	x		x	x	
Vital signs (pulse rate, respiratory rate, blood pressure, and temperature)	Section 8.2.2	x		x	x	
Complete physical examination, height, weight	Section 8.2.1	x				

Table 1 Schedule of Activities (cont.)

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
Limited physical examination, weight [h]	Section 8			x	x	
Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) [g, h]	Section 8.2.4 and Appendix 2		x	x	x	
Chemistry (bicarbonate or total carbon dioxide (if considered standard of care for the site), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH) [g, h]	Section 8.2.4 and Appendix 2		x	x	x	
Troponin I or T	Appendix 2	x		x	x	
CPK	Appendix 2	x		x	x	

Table 1 Schedule of Activities (cont.)

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
TSH, free T3 (or total T3), and free T4 [h]	Section 8.2.4 and Appendix 2	x		C1D1 and C4D1 and every fourth cycle thereafter (i.e., Cycles 1, 4, 8, and 12)	x	
C-reactive protein	Appendix 2			x (Only collected on C1D1, prior to first dose of study treatment)		
Coagulation tests: INR and aPTT [g, h]	Section 8.2.4 and Appendix 2		x		x	
MRI (preferred) or contrast CT of brain	Section 8.1.1	x				
Study Drug administration	Section 6.1			x		
Disease assessment, (CT chest and abdomen [including liver and adrenal glands] with contrast) [i]	Section 8.1.1		Disease assessments will be done at screening and every 16 weeks (± 14 days) starting at Cycle 1, Day 1 in the first year, every 26 weeks (± 4 weeks) during Years 2–5 and annually thereafter (low dose non-contrast CT recommended after 5 years). Disease assessments will continue per schedule regardless of whether study treatment is completed or held or discontinued (for any reason) until disease recurrence, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. All radiographic images must also be submitted to an IRF for a quality and completeness check and potential BICR.			
Patient-reported outcomes (PRO-CTCAE [select	Section 8.2.6 and Appendix 6			C1D1, C2D1, C3D1, and C4D1, C8D1, C12D1	x	

Table 1 Schedule of Activities (cont.)

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
items] and EORTC IL46) [j]						
Patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L) [j]	Section 8.1.2 and Appendix 6			C1D1, C2D1, C3D1 and C4D1, C8D1, C12D1	x	Approximately 3 and 6 months, at the survival follow-up
Adverse events	Section 8.3 and Appendix 3		x	x	x	
Serum PK sample (central laboratory)	Appendix 2			Refer to Appendix 2 for the PK sampling schedule		
Serum ADA sample (central laboratory)	Appendix 2			Refer to Appendix 2 for the ADA sampling schedule		
Blood sample for biomarkers (central laboratory)	Appendix 2			Refer to Appendix 2 for the biomarker sampling schedule		
Tumor biopsy, if clinically feasible	Section 8.7		Mandatory tumor biopsy, unless not clinically feasible, performed within 40 days after the first evidence of recurrence or prior to the next anti-cancer therapy, whichever is sooner.			

Table 1 Schedule of Activities (cont.)

Assessment/Procedure	Protocol Reference	Screening [a]		Treatment (28-Day Cycles)[b]	Treatment Discontinuation/ Completion [c]	Post-Treatment Follow-Up
		Days −28 to −1	Days −14 to −1	Day 1 (every 28 days) (± 3 days for Cycle ≥2)	≤30 Days After Final Dose	
Survival and anti-cancer therapy follow-up	Section 4					Approximately every 3 months (± 30 days) or more frequently until withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor

ADA = anti-drug antibody; ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; C = cycle; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; EBV = Epstein barr virus; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; Levels; FFPE = formalin fixed paraffin embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IL = item library; ratio; IRF = independent review facility; LC = lung cancer; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; PRO = participant-reported outcome.

[a] Screening tests and evaluations must be performed after the last dose of chemotherapy and within 28 days of randomization. Central PD-L1 tissue testing (and/or *EGFR* or *ALK* as applicable) may be performed prior to the last dose of chemotherapy after the pre-screening or the main ICF is signed. Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to randomization may be used (unless otherwise specified); such assessments do not need to be repeated for screening.

[b] Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments, and additional assessments may be performed if clinically indicated, as determined by the investigator.

[c] Participants may complete the treatment discontinuation/completion visit at the time of the last dose or confirmed disease recurrence, or return to the clinic no more than 30 days after the final dose of study treatment for a treatment discontinuation/completion visit.

Table 1 Schedule of Activities (cont.)

[d] Written informed consent is required for performing any study-specific tests or procedures. Signing of the ICFs can occur up to 60 days prior to randomization. Participants have the option to sign the Pre-Screening ICF to consent to PD-L1 tissue testing and/or *EGFR* or *ALK* testing (as applicable) prior to signing the main ICF.

[e] A representative FFPE tumor specimen (resection tumor tissues are preferred) in paraffin block (preferred) or at least 15–20 (5 additional slides must be provided if *ALK*/*EGFR* status is unknown) unstained, freshly cut, serial sections from an FFPE resected tumor specimen is required for participation in this study. Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed of if the quality of the submitted is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. This specimen must be accompanied by the associated pathology report.

[f] For participants with positive HBsAg, or participants with postive HBcAb in the absence of HBsAb, HBV DNA at screening, HBV DNA tests on Day 1 of every 3rd cycle (i.e., Cycles 3, 6, 9, 12), and at treatment discontinuation/completion. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to $>$ 500 IU/mL after initiation of study treatment, consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[g] Specified screening laboratory test results must be obtained within 14 days of randomization.

[h] Cycle 1, Day 1 must be performed within 5 days after the participant is randomized. ECOG performance status, limited physical examination, and local laboratory tests may be performed $\leq$ 96 hours before Day 1 of each cycle. Screening assessments performed $\leq$ 96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1.

[i] In rare cases where iodine contrast is contraindicated: CT chest non-contrast plus MRI abdomen preferred; CT chest/abdomen non-contrast acceptable.

[j] PROs will be completed before the participant receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study drug, whenever possible. PRO instruments will be self-administered by the participant at the investigational site, whenever possible. PROs may be collected remotely by telephone at the 3 and 6 month survival follow-up dates. In the event of a dose delay, PROs should not be re-administered for that cycle's visit.

Table 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type(s)
Day 1 of Cycle 1	Prior to co-infusion	Atezolizumab PK (serum)
		Tiragolumab PK (serum)
		Atezolizumab ADA (serum)
		Tiragolumab ADA (serum)
		Biomarker (Whole blood, Plasma, Serum) [a]
	30 (±10) minutes after end of co-infusion	Atezolizumab PK (serum)
		Tiragolumab PK (serum)
Day 1 of Cycles 2, 3, 4, 8, 13	Prior to co-infusion	Atezolizumab PK (serum)
		Tiragolumab PK (serum)
		Atezolizumab ADA (serum)
		Tiragolumab ADA (serum)
		Biomarker (Plasma and Serum) [a]
Select sites only: Day 1 of Cycles 6, 10	Prior to co-infusion	Biomarker (Plasma and Serum) [a, f]
Treatment discontinuation/completion visit [b]	At visit	Atezolizumab PK (serum)
		Tiragolumab PK (serum)
		Atezolizumab ADA (serum)
		Tiragolumab ADA (serum)
		Biomarker (Plasma and Serum) [a]
Optional: First post-treatment disease assessment (± 4 weeks) [c]	At disease assessment	Biomarker (Plasma and Serum) [a]
Optional: 6 and 12 months after treatment discontinuation/completion	At visit	Biomarker (Plasma and Serum) [a, d]
At the first evidence of disease recurrence (e.g,. at the same time as biopsy, if done)	At visit	Biomarker (Tumor Biopsy, Plasma, Serum) [a]
Any time point during the study (RBR consent required)		Optional RBR whole blood [e]

ADA = anti-drug antibody; C = cycle; D = day; NSCLC = non–small cell lung cancer; PK = pharmacokinetic; RBR = Research Biomarker Repository.

[a] Biomarker analysis may include exploratory biomarker research.

[b] Samples can be collected at the same time as the final dose or confirmed disease recurrence; otherwise the sample should be collected no more 30 days after the final dose.

[c] Samples will be collected only from participants who have not experienced confirmed disease recurrence yet.

[d] For the optional visits at 6 months or 12 months after treatment discontinuation/completion (or 6 months after first evidence of disease recurrence), the visit should be performed within ±3 weeks of the scheduled date. If the optional visit at 6 months aligns with the optional first post-treatment disease assessment visit, only one set of biomarker samples are required to be collected.

[e] The optional RBR whole blood sample requires an additional informed consent, and the sample can be collected at any time during the course of the study.

[f] Only at selected sites.

2. INTRODUCTION

2.1 STUDY RATIONALE

This is a Phase III, randomized, double-blind, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered to participants with PD-L1 positive (≥ 1% tumor cells [TC] by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA and select IIIB (T3N2) non–small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy.

2.1.1 Background on lung cancer

Lung cancer remains the leading cause of cancer deaths worldwide and is one of the most common cancers in both men and women (Torre et al. 2016; Siegel et al. 2022). In 2023 in the United States, it is estimated that there will be 238,340 new cases of lung cancer and 127,070 lung cancer deaths (American Cancer Society 2023). Data from Europe estimate that in 2023 there will be 159,057 lung cancer deaths (Malvezzi et al. 2023).

Non-small cell lung cancer is the predominant subtype of lung cancer, accounting for approximately 80%–85% of all cases (Osmani et al. 2018). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for approximately 40%–50% of all NSCLC, while squamous cell histology accounts for approximately 20%–30% of NSCLC (Osmani et al. 2018). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, and sarcomatoid carcinoma, and are of poorly differentiated histology.

The annual incidence rate of NSCLC in the US per 100,000 (2017) was 13.2, 3.8, 5.9, 2.5, and 19.6 for Stage I, II, IIIA, IIIB, and stage IV respectively (Ganti et al. 2021). Furthermore, in the U.S., the 5-year survival for those with localized disease at diagnosis (Stage I–II) is 59.0%, decreasing to 31.7% among those with regional (Stage III) disease and 5.8% among those with metastatic (Stage IV) disease (Thandra et al. 2021).

2.2 BACKGROUND

2.2.1 Treatment options for surgically resectable NSCLC

In its early stages, NSCLC is treated surgically with curative intent. However, 30%–70% of patients undergoing resection develop recurrence and die as a result of disease progression (Siegel et al. 2023). Radiation therapy is no longer recommended after surgery as an adjuvant treatment option for patients with Stage I and II NSCLC because it has been shown to have a deleterious effect on long-term survival (Pezzi et al. 2017).

For patients with Stage I disease with tumors measuring < 4 cm, surgical treatment alone is the standard of care (SOC). For Stage II to IIIB disease, the development of platinum-based chemotherapy has led to its use as adjuvant or neoadjuvant therapy

together with surgery to improve survival outcome compared with surgery alone. Chemotherapy regimens used in the adjuvant and neoadjuvant settings involve platinum-based doublets, which are similar to those used in metastatic settings. Agents that have been partnered with either cisplatin or carboplatin for the treatment of NSCLC include taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, etoposide and pemetrexed. Combinations of these drugs with platinum analogs are superior to single-agent therapy and have been shown to prolong survival, despite notably increased toxicity (Azzoli et al. 2009).

Recently, neoadjuvant and adjuvant approaches with either targeted or immunotherapy agents in combination or following chemotherapy for fully resected (Stage II to IIIB) NSCLC have been approved and are emerging as the next SOC (National Comprehensive Cancer Network [NCCN] 2023). In addition, several ongoing cancer immunotherapy (CIT) studies in the peri-operative setting (combining neo-adjuvant and adjuvant treatments) are ongoing.

2.2.1.1 Adjuvant Treatment for Surgically Resected NSCLC

Adjuvant Chemotherapy

Adjuvant chemotherapy is the SOC for fully resected (Stage II, IIIA, or select IIIB [T3N2]) NSCLC (8th edition TNM staging; Detterbeck et al. 2017) (see Appendix 7). The Lung Adjuvant Cisplatin Evaluation (LACE) reported on the results of a pooled analysis of data from five large Phase III trials comparing cisplatin-based adjuvant chemotherapy with no chemotherapy in participants with resected Stage I–III (7th edition TNM staging) NSCLC (Pignon et al. 2008). The analysis was designed to identify treatment options associated with a higher degree of benefit or groups of participants benefiting more from adjuvant treatment. With a median follow-up time of 5.2 years, the hazard ratio (HR) for overall survival (OS) was 0.89 (95% CI: 0.82 to 0.96; p=0.005), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. The survival benefit varied with stage, with the strongest effect seen in Stages II and III and a potential deleterious effect in Stage IA. The effect of chemotherapy on OS did not vary significantly (test for interaction with p=0.11) with the associated drugs, including vinorelbine (HR=0.80; 95% CI: 0.70 to 0.91), etoposide or vinca alkaloid (HR=0.92; 95% CI: 0.80 to 1.07), or other (HR=0.97; 95% CI: 0.84 to 1.13). In addition, there was no correlation between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy (RT), or planned total dose of cisplatin.

In the Phase III Cancer and Leukemia Group B 9633 study of adjuvant chemotherapy in Stage IB NSCLC, a survival advantage was not observed with paclitaxel and carboplatin in the intent-to-treat (ITT) Stage IB population (Strauss et al. 2008). However, exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for participants who had tumors ≥4 cm in diameter (HR=0.69; 95% CI: 0.48 to 0.99).

The Phase III adjuvant E1505 study and the JIPANG study suggest that platinum-based chemotherapy continues to be the current SOC in an unselected resectable patient population (Wakelee et al. 2017; Kenmotsu et al. 2020). The results from the E1505 study did not demonstrate improved disease-free survival (DFS) or OS with the addition of bevacizumab to platinum-based chemotherapy.

Adjuvant Postoperative Radiotherapy

Postoperative radiotherapy (PORT) is no longer recommended as a treatment option for patients with Stage I and II disease, because it has been shown to have a deleterious effect on long-term survival (PORT Meta-Analysis Trialists Group 1998). On the other hand, PORT may help improve locoregional recurrence rates and/or survival in carefully selected patients, such as those with pathologically confirmed N2 disease or positive surgical margins (Decker and Wilson 2008). In the Phase III LungART trial evaluating modern conformal PORT versus no PORT after complete resection of Stage IIIA N2+ NSCLC, no significant difference in 3-year DFS was observed (Le Péchoux et al. 2020). However, mediastinal relapse was reduced with PORT (25%) compared with the control arm (46%). The LungART trial results suggest that while PORT should not be recommended for all patients with completely resected Stage IIIA N2+ NSCLC, it is possible that select patients may benefit from PORT due to reduced risk of mediastinal relapse.

Adjuvant Targeted Therapy

For a select patients with resectable NSCLC, targeting a specific oncogenic driver,has been shown to improve upon the marginal benefit of platinum-based chemotherapy in the adjuvant setting. The ADAURA trial demonstrated that participants whose NSCLC had an epidermal growth factor receptor (EGFR) mutation achieved significant improvements in median DFS (HR=0.21; p< 0.0001) and overall survivial benefit (overall hazard ratio for death, 0.49; 95.03% CI, 0.34 to 0.70; P<0.001) with the addition of adjuvant osimertinib with or without platinum-based chemotherapy after surgery (Wu et al. 2020, Tsuboi et al. 2023).

There are other targeted therapies currenly under investigation in the adjuvant setting, including the Phase III ALINA study of alectinib versus chemotherapy as adjuvant therapy in participants with Stage IB–IIIA anaplastic lymphoma kinase-positive (ALK+) NSCLC.

Adjuvant Cancer Immunotherapy

Cancer immunotherapy (CIT) has transformed the treatment paradigm of solid tumors, including NSCLC, but until recently, approvals in NSCLC were limited to advanced or metastatic disease settings. Atezolizumab was the first CIT approved for the adjuvant treatment of early-stage resectable patients whose tumors have PD-L1 expression on≥ 1% of tumor cells (TC) (in the US, Japan and other countries) or PD-L1 expression

on ≥ 50% TC (in the EU and other countries) Stage II–IIIA NSCLC based on the IMpower010 trial (Atezolizumab U.S. Package Insert and Summary of Product Characteristic). At the planned interim analysis of the DFS primary endpoint, atezolizumab demonstrated a statistically significant improvement in DFS over best supportive care (BSC) in the Stage II–IIIA PD-L1 ≥ 1% TC analysis population with a HR of 0.66 (95% CI: 0.50 to 0.88, p = 0.0039). Median DFS was not reached (95% CI: 36.1, not estimable [NE]) in the atezolizumab arm and was 35.3 months (95% CI: 29.0 to NE) in the BSC arm (Felip et al. 2021). In the PD-L1 ≥ 50% TC Stage II–IIIA population, the unstratified HR was 0.49 (95% CI: 0.29 to 0.81) without *EGFR* mutations or *ALK* rearrangements. A later pre-specified exploratory analysis of OS suggested a trend in favor of atezolizumab over BSC in the PD-L1 ≥ 1% TC Stage II–IIIA population (stratified HR = 0.77; 95% CI: 0.51 to 1.17) and a clinically meaningful improvement in the PD-L1 ≥ 50% TC Stage II–IIIA population without *EGFR* mutations or *ALK* rearrangements (unstratified HR = 0.42; 95% CI: 0.23 to 0.78) was reported (Felip et al. 2021).

More recently adjuvant pembrolizumab received Food and Drug Administration (FDA) approval for participants with Stage IB (T2a ≥ 4 cm), Stage II, or Stage IIIA NSCLC regardless of PD-L1 expression based on the KN-091 trial (Pembrolizumab U.S. Package Insert). At the protocol specified second interim analysis, pembrolizumab demonstrated a statistically significant DFS improvement over placebo in the Stage IB–IIIA overall population with a HR of 0.76 (95% CI: 0.63 to 0.91, p = 0.0014). Median DFS was 53.6 months (95% CI: 39.2 to not reached [NR]) in the pembrolizumab arm and was 42.0 months (95% CI: 31.3 to NR) in the placebo arm (O'Brien et al. 2022). Notably, the dual primary endpoint of DFS in the PD-L1 ≥ 50% tumor proportion score (TPS) population was not significant. Median DFS was not reached for the pembrolizumab arm (95% CI: 44.3 to NR) or the placebo arm (95% CI: 35.8 to NR) with a HR of 0.82 (95% CI: 0.57 to 1.18; p = 0.14). The limited benefit in the PD-L1 ≥ 50% TPS population in KN-091 was in contrast with the results from the IMpower010 study and the experience in the locally advanced or metastatic setting for both atezolizumab and pembrolizumab, where higher PD-L1 expression correlated with increasing benefit (Herbst et al. 2016; Mok et al. 2019; Felip et al. 2021).

2.2.1.2 Neoadjuvant and Perioperative Treatment for Surgically Resectable NSCLC

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is another approach for the treatment of resectable NSCLC, with survival benefits comparable to those achieved with adjuvant chemotherapy. A meta-analysis reported an indirect comparison of neoadjuvant and adjuvant chemotherapy and concluded that there were no differences in both OS and DFS between neoadjuvant and adjuvant chemotherapy (Lim et al. 2009). The data included 32 randomized trials (10 neoadjuvant and 22 adjuvant) involving more than 10,000 participants. For OS, the HR of adjuvant chemotherapy compared with

neoadjuvant chemotherapy was 0.99 (95% CI: 0.81 to 1.21), and for DFS, the HR was 0.96 (95% CI: 0.77 to 1.20).

A review of 15 neoadjuvant trials showed an absolute survival improvement of 5% at 5 years and a 13% reduction in the relative risk of death (OS HR=0.87; 95% CI: 0.78 to 0.96) with neoadjuvant chemotherapy compared with surgery alone (NSCLC Meta-Analysis Collaborative Group 2014). There were no notable differences in survival between different chemotherapy regimens or scheduling, platinum agents, age, sex, performance status, histology, and whether or not PORT was given. Time-to-distant recurrence was also significantly longer for participants who received neoadjuvant treatment versus surgery alone (HR=0.69; 95% CI: 0.58 to 0.82).

Neoadjuvant and Peri-Operative Cancer Immunotherapy

With the successful development of CIT in advanced NSCLC, several neoadjuvant and peri-operative studies of anti-PD-L1/ programmed death−1 (PD-1) inhibitors (atezolizumab, nivolumab, pembrolizumab, and durvalumab) are currently being conducted in resectable NSCLC.

Nivolumab in combination with platinum-based chemotherapy was the first CIT to receive FDA approval in the neoadjuvant setting (OPDIVO® U.S. Package Insert). This approval was based on the CheckMate-816 trial (Forde et al. 2022). The two primary endpoints were event free survival (EFS) and pathological complete response (pCR). With a minimum of 21 months follow up, nivolumab plus chemotherapy demonstrated a statistically significant improvement in EFS over chemotherapy alone in the primary analysis population (Stage IB−IIIA) with a HR of 0.63 (95% CI: 0.43 to 0.91, p=0.005). Median EFS was 31.6 months (95% CI: 30.2 to NR) with nivolumab plus chemotherapy and 20.8 months (95% CI: 14.0 to 26.7 months) with chemotherapy alone. Statistically significant improvement in pCR was observed (OR=13.94 [99% CI: 3.49 to 55.75]; p<0.0001) with 24% of participants in the nivolumab plus chemotherapy arm achieving pCR compared with 2.2% of participants in the chemotherapy alone arm. pCR benefit was consistent across disease stages, histologies, and PD-L1 expression levels.

Recent data from two studies, where CIT was given peri-operatively, also show promise. In the AEGEAN study, comparing neoadjuvant durvalumab plus chemotherapy followed by adjuvant durvalumab monotherapy versus neoadjuvant chemotherapy alone statistically significant EFS and pCR benefit was observed with 11.7 months median follow up (Heymach et al. 2022). Median EFS was not reached in the durvalumab-based regimen arm (95% CI: 31.9 to NR) versus 25.9 months in the chemotherapy arm (95% CI: 18.9 to NR) with a HR of 0.68 (95% CI: 0.53 to 0.88, p=0.003902). Statistically significant improvement in pCR rate was observed (difference in pCR rate: 13.0% [95% CI: 8.7 to 17.6]; p=0.000036) with 17.2% of participants in the durvalumab-based regimen achieving pCR compared with 4.3% of participants in the chemotherapy alone arm.

In the KEYNOTE-671 study, comparing neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy versus neoadjuvant placebo plus chemotherapy followed by adjuvant placebo, statistically significant EFS (dual primary endpoint together with OS) was observed with 25.5 months median follow up (Wakelee et al. 2023). Median EFS was not reached in the pembrolizumab-based regimen arm (95% CI: 34.1 to NR) versus 17.0 months in the chemotherapy arm (95% CI: 14.3 to 22.0 months) with a HR of 0.58 (95% CI:0.46 to 0.72, $p < 0.001$). At this analysis, OS was still immature, as the estimated 24-month OS was 80.9% in the pembrolizumab-based regimen and 77.6% in the chemotherapy arm ($p = 0.02$, which did not meet the significance criterion).

Other peri-operative trials are still ongoing, including IMpower030 (comparing neoadjuvant atezolizumab plus chemotherapy followed by adjuvant atezolizumab monotherapy versus neoadjuvant placebo plus chemotherapy followed by adjuvant placebo) and CheckMate-77T (comparing neoadjuvant nivolumab plus chemotherapy followed by adjudvant nivolumab monotherapy versus neoadjuvant placebo plus chemotherapy followed by adjuvant placebo).

2.2.2 Study Drug Background

Background on blockade of the TIGIT pathway in cancer as a potential anti-cancer therapy

TIGIT is an immune inhibitory receptor that is a member of the Ig super family (Yu et al. 2009; Chiang and Mellman 2022). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is coordinately expressed with other checkpoint immune receptors such as PD-1 and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T-cells and NK-cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (TCs) (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including NSCLC, and is highly correlated with T-cell infiltration and PD-1 expression (Johnston et al. 2014). Fluorescence-activated cell sorting analysis of fresh tumor samples showed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells. TIGIT expression ranges from 30% to 80% and from 50%–80% on tumor-infiltrating $CD4+$ and $CD8+$ T cells, respectively (Johnston et al. 2014). It has also been reported that tumor-infiltrating lymphocytes from early-stage primary NSCLCs co-express TIGIT with PD-1, suggesting that TIGIT expression may be important throughout the development of NSCLC (Tassi et al. 2017).

Therefore, TIGIT is a potential target for therapeutic intervention aimed at restoring the immune response against the tumor, especially in NSCLC. Agents that inhibit the activity of TIGIT may relieve an important source of tumor-associated immune

suppression and may enhance the activity of other immune-based therapies, such as atezolizumab, an inhibitor of PD-L1. Preclinical and biomarker data support a non-canonical mechanism of action with dual checkpoint blockade, which suggests that blocking TIGIT not only activates the T cells but also modifies the tumor resident Tregs and tumor associated macrophages that in turn support T cell activation (Patil et al. 2023). Early nonclinical results using genetically deficient mice and blocking antibodies reveal a key role for TIGIT in regulating T-cell responses. Mechanistically, combination of TIGIT with PD-L1 or PD-1 blockade unleashes signaling through activating co-stimulatory receptors to generate optimal anti-tumor CD8+ T-cell responses (Banta et al. 2022). Together the data support the hypothesis that anti-TIGIT in combination with anti-PD-L1 may reactivate anti-tumor immunity in NSCLC to provide clinical benefit to participants.

Combined inhibition of the TIGIT and PD-L1/PD-1 pathways as a potential anti-cancer therapy

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target TCs. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with TIGIT-PVR interaction may enhance the magnitude and quality of the tumor-specific T-cell responses through increased expansion of T cells as well as improved T-cell priming and/or effector function. Because TIGIT and PD-1 are co-expressed by infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab.

The combined inhibition of the TIGIT and PD-L1/PD-1 pathways by tiragolumab and atezolizumab, respectively, has demonstrated promising clinical activity in the Phase I Study GO30103 and the Phase II Study GO40290 (hereafter referred to as CITYSCAPE). Study GO30103 is a first-in-human, combined Phase Ia/Phase Ib open-label, dose-escalation, multicenter study. The study evaluated the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of tiragolumab administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) to participants with locally advanced or metastatic malignancies. As of 1 October 2021, 200 participants with multiple tumor types, including NSCLC, had been enrolled in the Phase Ib portion of the study. Objective responses, including complete responses (CR) in 4 participants, and partial responses (PR) in 25 participants, have been observed.

No maximum tolerated dose (MTD), no dose-limited toxicities (DLTs), and no clear dose-related trends in the incidence or severity of adverse events have been determined for single-agent tiragolumab or tiragolumab in combination with atezolizumab in Study GO30103.

Tiragolumab was further evaluated in participants with PD-L1 selected advanced NSCLC (≥ 1% tumor proportion score [TPS]) in the Phase II, global, randomized, double-blind, placebo-controlled CITYSCAPE study. At the primary analysis, the confirmed objective response rate (ORR) in the ITT population was higher in the tiragolumab combined with atezolizumab arm (31.3%) than in the placebo combined with atezolizumab arm (16.2%). Investigator-assessed progression-free survival (PFS) was also improved with a stratified HR of 0.57 (95% CI: 0.37 to 0.90), with a median PFS of 5.4 and 3.6 months in the tiragolumab combined with atezolizumab arm compared to the placebo combined with atezolizumab arm, respectively. Responses to tiragolumab in combination with atezolizumab were observed in participants with both squamous and non-squamous histology (Cho et al. 2022).

In CITYSCAPE, as of 16 August 2021, there were 135 safety-evaluable participants. The safety profile was comparable between the tiragolumab combined with atezolizumab arm and the placebo combined with atezolizumab arm for all grades of adverse events (98.5% vs. 97.1%), Grade 3–4 adverse events (52.2% vs. 39.7%), Grade 5 adverse events (4.5% vs. 10.3%), serious adverse events (52.2% vs. 41.2%), and adverse events leading to study treatment withdrawal (14.9% vs. 13.2%). Study treatment-related adverse events occurred at a higher frequency in the tiragolumab combined with atezolizumab arm (82.1%) compared with the placebo combined with atezolizumab arm (70.6%).

Using a comprehensive medical concepts strategy, immune-mediated adverse events were reported with a higher frequency in the tiragolumab combined with atezolizumab arm (69%) compared to the placebo combined with atezolizumab arm (47%). The difference (≥10% difference between arms) was predominantly attributed to events of immune-mediated rash (preferred terms of rash, rash maculopapular, dermatitis, erythema, eczema, pruritic rash, folliculitis and skin ulcer) (40% vs. 15%) and infusion-related reactions (IRR) (preferred term of infusion-related reaction) (30% vs. 10%)

Tiragolumab is being investigated in clinical studies as a potential therapy against various tumor types. Refer to the Tiragolumab Investigator's Brochure for details on the nonclinical and clinical studies for tiragolumab.

Background on Tiragolumab

Tiragolumab is a fully human IgG1/κ mAB that binds T-cell immunoreceptor with Ig and ITIM domains (TIGIT), an immune inhibitory receptor that is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as poliovirus receptor [PVR]) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for

cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is combined with other CIT and chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in participants with cancer.

Refer to the Tiragolumab Investigator's Brochure for details on the nonclinical and clinical studies for tiragolumab.

Background on Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody (mAB) that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows antitumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies.

Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and CIT.

Atezolizumab is approved globally for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma. Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies and country specific approvals.

2.3 BENEFIT–RISK ASSESSMENT

Study Rationale

This study is designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in participants with resected, Stage IIB, IIIA, or select IIIB (T3N2 only) (AJCC 8th edition) PD-L1 positive (≥1% TC by investigational VENTANA PD-L1 (SP263) CDx assay) NSCLC who have received adjuvant platinum-based chemotherapy.

The IMpower010 study, with atezolizumab, was the first to demonstrate that adjuvant CIT following resection and adjuvant platinum-based chemotherapy provides clinical benefit in participants with resectable NSCLC that are PD-L1≥1% TC. With the recent

approvals for adjuvant (atezolizumab and pembrolizumab) and neoadjuvant (nivolumab) treatment approaches and with the recent encouraging data emerging for pre-operative treatment regimens, progress has been made for resectable NSCLC after more than a decade of little to no improvement in the treatment landscape. However a significant proportion of participants still experience disease re-occurrence; hence, continued research of novel candidates and combinations are warranted.

In the primary analysis of CITYSCAPE, in all randomized participants whose lung cancer had a PD-L1 $\geq$1% TPS/TC (n=135), the confirmed ORR was higher in the tiragolumab plus atezolizumab group (31.3%) than in the placebo plus atezolizumab group (16.2%) (Cho et al 2022). Furthermore, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group (n=67) relative to placebo plus atezolizumab group (n=68) (stratified HR=0.57; 95% CI: 0.37 to 0.90; median PFS 5.4 vs. 3.6 months, respectively). At an updated analysis, the median OS in the intention-to-treat population was 23.2 months in the tiragolumab plus atezolizumab group compared to 14.5 months in the placebo plus atezolizumab group (stratified HR 0.69 [95% CI: 0.44 to 1.07], p=0.093).

Consistent with the Phase Ib portion of Study GO30103, the combination of atezolizumab with tiragolumab was tolerated in the CITYSCAPE study (for more details, refer to the Tiragolumab Investigator's Brochure). Atezolizumab plus tiragolumab demonstrated an overall safety profile similar to that of atezolizumab alone in terms of all Grade adverse events, Grade 3 and 4 adverse events, serious adverse events and adverse events leading to study treatment discontinuation. While adverse events related to any study treatment and adverse events leading to dose interruption of any study treatment were higher in the tiragolumab plus atezolizumab arm, there was no increase in Grade 5 adverse events (see the Tiragolumab Investigator's Brochure). Adverse events with potentially immune-mediated causes have been observed with a higher frequency for tiragolumab in combination with atezolizumab in CITYSCAPE. However, the imbalance was mostly attributed to Grade 1 and 2 rashes and IRRs. Grade 3 and 4 immune-mediated adverse events were similar between the tiragolumab plus atezolizumab treatment group compared with atezolizumab treatment alone. To date, immune-mediated adverse events have been manageable with standard medical practice supplemented with corticosteroids, immunosuppressive agents, and/or hormone replacement therapy.

In the Phase III SKYSCRAPER-01 study, patients with previously untreated PD-L1 high ($\geq$50% TPS/TC), locally advanced or metastatic NSCLC were randomized to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab with the co-primary endpoints of OS and investigator assessed PFS. At the recent first interim analysis, although the study did not meet its co-primary endpoint of progression-free survival, and the other co-primary endpoint of OS was immature, a numerical improvement was observed in both co-primary endpoints (Genentech press release, 2022). Tiragolumab

plus atezolizumb was well-tolerated, and no new safety signals were identified when adding tiragolumab. The study will continue until the next planned analysis.

In light of the evidence of clinical activity of atezolizumab plus tiragolumab in NSCLC, the favorable safety profile of the combination to date, and the demonstrated efficacy and approval of adjuvant atezolizumab in resectable NSCLC; the Sponsor is conducting this Phase III Study GO45006. This study addresses the need to decrease recurrence rates and improve survival for patients with resectable NSCLC.

Benefit-Risk Assessment

Data from CITYSCAPE indicate that combination therapy of atezolizumab plus tiragolumab may confer increased efficacy benefit in NSCLC relative to atezolizumab alone. Participants who received atezolizumab and tiragolumab as participants in the Phase Ib portion of Study GO30103 (solid tumors, including metastatic NSCLC), in the SKYSCRAPER-01 study (in metastatic NSCLC) also achieved encouraging efficacy outcomes. Given that the addition of tiragolumab to atezolizumab improved efficacy outcomes in metastatic NSCLC in CITYSCAPE, it is anticipated that this combined regimen may potentially also improve efficacy in resectable NSCLC. There are ongoing Phase Ib, II, and III studies investigating the combination of atezolizumab and tiragolumab, with and without platinum-based chemotherapy in lung cancer, which will generate additional safety and efficacy data as this study is enrolling (refer to the Tiragolumab IB for full list of ongoing studies).

The combination of atezolizumab plus tiragolumab was tolerated in Studies GO30103, CITYSCAPE, and SKYSCRAPER-01. The toxicities of atezolizumab alone and the combination of atezolizumab plus tiragolumab are expected to be similar. Immune-mediated adverse events, although reported at a higher frequency for the atezolizumab plus tiragolumab arm in CITYSCAPE, were generally mild, transient, monitorable, and manageable in nature. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tiragolomab and atezolizumab may be found in the tiragolumab IB and the atezolizumab prescribing information.

This study includes eligibility criteria, baseline measurements, and recommendations for management of adverse events, including guidelines for dose modifications, delays, and discontinuation of one or more of the study drugs that are designed to enhance the safety of participants in this trial. Refer to Appendix 4 for information on anticipated risks for tiragolumab and atezolizumab and risk mitigation measures, including guidelines for managing adverse events associated with tiragolumab and atezolizumab.

Oversight of this study will be provided by the Sponsor's Medical Monitor (see Section 8.10.9). Additionally, an independent data monitoring committee (iDMC), consisting of external experts, will be formed to evaluate safety data during the study.

Given the continued unmet need, the strength of the scientific hypothesis of and compelling clinical data supporting this study as well as the rigorous safety monitoring proposed, Study GO45006 will provide an evaluation of the benefit-risk profile of adjuvant atezolizumab plus tiragolumab following platinum-based chemotherapy.

This trial will enroll participants with Stage IIB, IIIA, or select IIIB NSCLC who have had a complete resection and received adjuvant platinum-based chemotherapy. Given the relatively poor prognosis and desired improvement in clinical outcomes, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with tiragolumab following surgery and platinum-based chemotherapy is expected to be acceptable in this setting.

COVID-19 Related Benefit-Risk Assessment

In the setting of the coronavirus 2019 (COVID-19) pandemic, participants with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-L1/PD-1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-L1/PD-1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by CIT.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a participant develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing participants with pulmonary symptoms.

Given the mechanism of action for atezolizumab and tiragolumab, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these two agents.

There are limited data concerning the possible interactions between CIT treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all participants with cancer receiving active therapy (including immune CPI), with the understanding that there are limited safety and efficacy data in such participants (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in participants who are receiving CIT (SITC 2020). For participants enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a participant should be made on an individual basis by the investigator in consultation with the participant.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for participants receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the participant and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 6.8.1)

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in participants with resected, Stage IIB, IIIA, or select IIIB (T3N2 only) (AJCC 8th edition) PD-L1 positive (≥1% TC by investigational VENTANA PD-L1 [SP263] CDx assay) and PD-L1 high (≥50% TC by investigational VENTANA PD-L1 (SP263) CDx assay) NSCLC who have received adjuvant platinum-based chemotherapy. Table 3 presents the primary objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (ICH 2020)

and select secondary objective and corresponding endpoints. Table 4 presents the other secondary and exploratory objectives and corresponding endpoints.

Table 3 Primary and Secondary Objectives and Corresponding Estimands/Endpoints

Primary Objectives	Estimand definitions
• To evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in the PD-L1 ≥ 50% TC and PD-L1 ≥ 1% TC populations	• Disease-Free Survival, as assessed by investigator, in the PD-L1 ≥ 50% TC population. The estimand for investigator-assessed DFS is defined as follows: – Population: Participants with completely resected tumors with PD-L1 high (≥ 50% TC by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA, or select IIIB NSCLC who have received adjuvant chemotherapy – Variable: Time from randomization to the occurrence of local/regional or distant recurrence of NSCLC, new primary NSCLC, or death from any cause (whichever occurs first), as determined by the investigator – Treatment: ▪ Tiragolumab plus atezolizumab: tiragolumab 840 mg plus atezolizumab 1680 mg administered by IV co-infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles, approximately 1 year ▪ Placebo plus atezolizumab: placebo plus atezolizumab 1680 mg administered by IV co-infusion on Day 1 of each 28-day cycle for a maximum of 13 cycles, approximately 1 year – Intercurrent events: ▪ Early discontinuation from study treatment for any reason: a treatment policy strategy will be used ▪ Start of non-protocol anti-cancer therapy prior to the respective event of interest: a treatment policy strategy will be used – Population-level summary: Hazard ratio for DFS • DFS, as assessed by investigator, in the PD-L1 ≥ 1% TC population. The estimand is defined the same way as for investigator-assessed DFS in the PD-L1 ≥ 50% TC population, except for the following: – Population: Participants with completely resected PD-L1 positive (≥ 1% TC by investigational VENTANA PD-L1 (SP263) CDx assay) Stage IIB, IIIA, or select IIIB NSCLC who have received adjuvant chemotherapy

Table 3 Primary and Secondary Objectives and Corresponding Estimands/Endpoints (cont.)

Secondary Objectives	Endpoint definition
• To 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 v5.0
• To evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Overall Survival • 3-year, 5-year, and 7-year DFS rates
• To evaluate the health-related quality of life of participants treated with tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Health-related quality of life on the basis of proportion of participants who maintain or meaningfully improve from baseline in patient-reported role, emotional, and physical functioning and GHS/QOL over the course of treatment.

CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease-free survival; GHS/QOL = Global health status and quality of life; HRQol = Health-related quality of life; NCI = National Cancer Institute; NSCLC; OS = overall survival; TC = tumor cells; V = version.

Table 4 Other Secondary and Exploratory Objectives and Endpoints

Other Secondary Objectives	Corresponding Endpoints
• To characterize the PK of tiragolumab plus atezolizumab	• Serum concentration of tiragolumab at specified timepoints • Serum concentration of atezolizumab at specified timepoints
• To evaluate the immune response to tiragolumab and 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
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate patient-reported HRQoL, functioning, and symptoms of tiragolumab plus atezolizumab compared with placebo plus atezolizumab	• Actual scores and change from baseline in patient-reported HRQoL, functioning, and symptoms as assessed through the use of the EORTC QLQ-C30 and QLQ-LC13 during the study

Table 4 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Exploratory Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate patient-reported tolerability of tiragolumab plus atezolizumab compared with placebo plus atezolizumab from the participant's perspective	• Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities, as assessed through use of the NCI PRO-CTCAE (selected items) during study treatment • Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE (selected items) during study treatment • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC IL-46
• To evaluate potential effects of ADAs	• Relationship between tiragolumab ADA status and/or atezolizumab ADA status and efficacy, safety, or PK endpoints
• To identify and/or evaluate biomarkers that may correlate with clinical benefit to tiragolumab plus atezolizumab compared with placebo plus atezolizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to tiragolumab plus atezolizumab compared with placebo plus atezolizumab, can provide evidence of tiragolumab plus atezolizumab compared with placebo plus atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in tumor tissues and blood and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
• To evaluate health status utility scores of participants treated with tiragolumab plus atezolizumab compared with atezolizumab	• Actual scores and change from baseline in EQ-5D-5L index-based and VAS scores at specified timepoints during the study

ADA = anti-drug antibodies; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; IL-46 = Item Library; HRQoL = Health-related quality of life; NCI = National Cancer Institute; PK = pharmacokinetics; PRO = Participant-Reported Outcomes; VAS = visual analog scale.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase III, randomized, double-blind, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered in participants with PD-L1 ≥ 1% TC Stage IIB, IIIA, or select IIIB (T3N2 only) NSCLC following resection and adjuvant platinum-based chemotherapy.

The study schema is shown in Figure 1 (Section 1.2). The schedule of activities is provided in Table 1 (Section 1.3). The PK, immunogenicity, and biomarker sampling schedules are presented in Table 2 (Section 1.3).

Male and female participants age ≥ 18 years old with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have had a complete surgical resection of Stage IIB, IIIA, or select IIIB (T3N2 only) NSCLC with PD-L1 ≥ 1% TC expression, followed by adjuvant platinum-based chemotherapy, with no evidence of recurrent disease, are eligible.

Screening tests and evaluations, except central PD-L1 tissue testing (and/or EGFR or ALK as applicable), must be performed after the last dose of chemotherapy and within 28 days of randomization. Participants have the option to sign the Pre-Screening informed consent form (ICF) to consent to PD-L1 tissue testing and/or *EGFR* or *ALK* testing (as applicable) prior to signing the main ICF for all screening procedures and study participation. After providing informed consent, participants will undergo screening procedures as outlined in the schedule of activities.

During pre-screening or screening, tumor tissue from each potentially eligible participant will be tested for PD-L1 expression by a central laboratory using the investigational VENTANA PD-L1 (SP263) CDx Assay. Only participants with PD-L1 expression ≥ 1% TC by the investigational VENTANA PD-L1 (SP263) CDx assay are eligible for enrollment.

Participants whose tumors have a known *EGFR* mutation or *ALK* rearrangement will be excluded from enrollment in this study. Participants with non-squamous NSCLC who have an unknown *EGFR* or *ALK* status will be required to be tested at screening. Participants with squamous NSCLC who have unknown *EGFR* or *ALK* status are eligible and will not be required to be tested at pre-screening or screening. *EGFR* and/or *ALK* status may be assessed locally or at a central laboratory.

Approximately 1150 (approximately 700 [60%] with PD-L1 ≥ 50% TC and approximately 450 [40%] with PD-L1 1%–49% TC) participants will be enrolled in the study. Enrollment of a specific PD-L1 population will be capped once it hits its specified target. Participants who discontinue study treatment prematurely will not be replaced.

Randomization must be completed at the latest 70 days after the final dose of chemotherapy. Eligible participants will be randomized in a 1:1 ratio to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab. Participants should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days of randomization.

Eligible participants will be stratified by tumor histology (squamous vs. non-squamous), disease stage (Stage IIB vs. Stage IIIA+ select IIIB [T3N2 only]) and PD-L1 status (1%–49% TC vs. ≥50% TC). Enrollment into the PD-L1 1%–49% TC sub-group will be capped at approximately 450 (40%) participants and enrollment into the PD-L1 ≥50% TC sub-group will be capped at approximately 700 (60%) participants.

In the experimental arm, tiragolumab 840 mg plus atezolizumab 1680 mg will be administered by IV co-infusion (tiragolumab and atezolizumab will be mixed and administered in one IV bag) on Day 1 of each 28-day cycle for a total of 13 cycles, approximately 1 year. In the comparator arm, placebo plus atezolizumab 1680 mg will be administered by IV co-infusion on Day 1 of each 28-day cycle for a total of 13 cycles, approximately 1 year.

Crossover from the placebo plus atezolizumab arm to the tiragolumab plus atezolizumab arm will not be allowed.

Treatment will be continued for a maximum of 13 cycles, approximately 1 year, in the absence of disease recurrence, or unacceptable toxicity.

All participants will undergo scheduled disease assessment scans by computed tomography (CT) at screening and every 16 weeks (±2 weeks) starting at Cycle 1, Day 1 in the first year, every 26 weeks (± 4 weeks) in Years 2–5, and annually thereafter (low-dose non-contrast CT recommended after 5 years). Disease assessments will continue per schedule regardless of whether study treatment is completed or held or discontinued (for any reason) until disease recurrence, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Disease recurrence must be determined radiographically as evidenced by local/regional recurrence, distant metastasis, or a second primary NSCLC (see Section 8.1.1). If a disease assessment shows disease recurrence, it must be confirmed pathologically, unless not clinically feasible.

Safety assessments will include the incidence, nature, and severity of adverse events, graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

Participants will be asked to complete PRO questionnaires during study treatment, at treatment discontinuation/completion, and at 3 and 6 months post-treatment during follow-up. PROs will be completed before the participant receives any information on

disease status and prior to the performance of non-PRO assessments and the administration of study drug, whenever possible. PRO instruments will be self-administered by the participant at the investigational site, whenever possible. PROs may be collected remotely by telephone at the 3 and 6 month survival follow-up dates. In the event of a dose delay, PROs should not be re-administered for that cycle's visit.

Serum samples will be collected to monitor atezolizumab and tiragolumab pharmacokinetics and to detect the presence of antibodies to atezolizumab and tiragolumab. Participant samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for exploratory biomarker assessments.

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first. Serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of new anti-cancer therapy. After this period, investigators should report serious adverse events that are believed to be related to prior treatment with study drug(s). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

After discontinuation of treatment, participants will enter the post-treatment follow-up period of the study. Post-treatment follow-up will consist of ongoing assessments as described above and as detailed in the schedule of assessments. Follow-up information, including survival and new anti-cancer therapy information, will be collected by means of telephone calls, participant medical records, and/or clinic visits until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. If the participant requests to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator. If a participant withdraws consent from survival follow-up, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

An iDMC (independent data monitoring committee) will be formed to evaluate safety data on a periodic basis as well as to review the interim analyses of investigator-assessed DFS. 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.

Radiographic images will be submitted to an independent review facility (IRF) for a quality and completeness check, for potential blinded independent central review (BICR), and for temporary storage prior to transferring images to the Sponsor for the long-term retention.

4.2 RATIONALE FOR STUDY DESIGN

This is a Phase III, randomized, double-blind, global, multicenter study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered to participants with PD-L1 ≥ 1% TC Stage IIB, IIIA and select IIIB (T3N2) NSCLC following resection and adjuvant platinum-based chemotherapy.

4.2.1 Rationale for Study Population

This study will enroll participants with PD-L1 ≥ 1% TC Stage IIB, IIIA and select IIIB (T3N2) NSCLC. With CIT and targeted therapies becoming available for resectable NSCLC, treatment options for some patients have improved over chemotherapy based regimens. Nevertheless, a significant proportion of patients will still experience disease recurrence and will die from their disease, highlighting the need to continue to build on the recent successes.

4.2.1.1 Rationale for Including Participants with PD-L1 ≥ 1% TC Status

In the IMpower010 study, adjuvant atezolizumab demonstrated a statistically significant DFS benefit over best supportive care in participants with Stage II–IIIA NSCLC whose tumors expressed PD-L1 on ≥ 1% TC (HR 0.66, 95% CI: 0.50 to 0.88: p = 0.039) (Felip et al. 2021). Furthermore, recent clinical data in the neo-adjuvant and the peri-operative setting support benefit of PD-L1/PD-1 inhibition across PD-L1 subgroups in resectable NSCLC (Forde et al. 2022; Wakelee et al. 2023) Taken together, these data suggest that patients whose tumors are PD-L1 positive, may benefit from PD-L1/PD-1 blockade in the resectable NSCLC setting

In the current study, tiragolumab will be added to atezolizumab to potentially improve upon the benefit seen in IMpower010. As discussed in Section 2.2.2, the combination of tiragolumab with atezolizumab may enhance the activity seen with adjuvant atezolizumab by relieving tumor-associated immune suppression and creating an optimal anti-tumor T cell environment (Banta et al. 2022; Patil et al. 2023).

4.2.1.2 Rationale for Including Only Participants with Stage IIB, IIIA and select IIIB (T3N2) disease

In IMpower010, clinical benefit of adjuvant atezolizumab over best supportive care following adjuvant platinum-based chemotherapy was demonstrated in the Stage IIA–IIIA NSCLC (AJCC 7th edition) population (Felip et al. 2021). Stages IIA-IIIA by AJCC 7th edition correspond to Stages IIB, IIIA, and select IIIB (T3N2) disease by AJCC 8th edition staging. This study aims to evaluate additional clinical benefit from

combination therapy of tiragolumab plus atezolizumab over atezolizumab alone, and thus will include a similar population.

4.2.1.3 Rationale for Exclusion of Participants with an EGFR Mutation or ALK Rearrangement

Patients with known EGFR mutations or ALK rearrangement will be excluded, because the likelihood of benefit is uncertain, and data continue to emerge suggesting that immunotherapies do not bring the same benefit to patients with EGFR mutations or ALK rearrangements as they do to patients without these genomic alterations (Borghai et al. 2015; Herbst et al. 2016). NCCN guidelines for adjuvant use of atezolizumab in NSCLC direct patients with EGFR/ALK-positive NSCLC away from treatment with atezolizumab or other immunotherapy accordingly (National Comprehensive Cancer Network [NCCN] 2023). Additionally, the ADAURA trial has established osimertinib as the standard of care adjuvant therapy for *EGFR*-mutated NSCLC (Wu et al 2020).

4.2.2 Rationale for Primary Endpoint

While OS is the gold standard for establishing benefit in oncology clinical trials, the time necessary for an OS readout in the adjuvant NSCLC setting could lead to an unacceptable delay in making a new effective therapy available to participants. DFS (the primary efficacy endpoint in this study) is a meaningful and reliable efficacy endpoint with earlier time to evaluation compared to OS. DFS appears strongly correlated with OS in the adjuvant NSCLC setting, as demonstrated in several meta-analyses with chemotherapy (Michiels et al. 2011; Mauguen et al. 2013). Furthermore, DFS is recommended by the FDA as a surrogate endpoint for both accelerated and traditional approval and has as such been used as the primary basis for approval for adjuvant therapy in several indications including for adjuvant CIT in NSCLC (FDA Guidance to Industry, 2018; and KEYTRUDA® U.S. Package Insert).

Secondary efficacy endpoints, including DFS rates at specific timepoints and OS, will provide supportive measures of efficacy.

4.2.3 Rationale for Biomarker Sample Collection

Tumor Tissue Biomarker Assessment

Collection of tumor tissue specimens is required for this study to determine PD-L1 status for participant selection at $\geq$1% TC as determined by investigational VENTANA PD-L1 (SP263) CDx assay by central testing. Published results suggest that the expression of PDL1 in tumors correlates with response to anti-PD-L1 and anti-PD-1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In IMpower010, PD-L1 inhibition demonstrated a statistically significant improvement in disease free survival in the PD-L1$\geq$1% TC population, with the greatest benefit observed in the PD-L1 $\geq$ 50% TC sub-group (Felip et al. 2021).

In addition to the assessment of PD-L1, other exploratory biomarkers may be evaluated in tumor tissue to investigate potential predictive and prognostic features that may be associated with clinical benefit to tiragolumab and/or atezolizumab or resistance to therapy. The availability of a larger dataset will assist in identification and characterization of candidate biomarkers and biological hypotheses that may inform evaluation of novel combinations, participant selection, and/or future study designs.

Blood Biomarker Assessment

An exploratory objective of this study is to evaluate surrogate biomarkers for efficacy that may include circulating-tumor DNA (ctDNA), gene expression, circulating proteins, and other analytes in blood samples. Evaluation of blood biomarkers may provide further evidence for distinct biologic activity of tiragolumab and/or atezolizumab combination in participants with NSCLC and may allow for the development of blood-based biomarkers to help predict which participants are more likely to benefit from tiragolumab plus atezolizumab.

Whole genome sequencing (WGS) or whole exome sequencing (WES) of blood and tissue samples will be conducted to identify somatic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood will be compared with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomics is increasingly informing researcher's understanding of disease pathobiology. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

4.2.4 Rationale for the Collection of Tumor Specimens at Disease Recurrence and/or Confirmation of a New Primary NSCLC

Initial apparent disease recurrence may occur as a result of either delayed anti-tumor activity and/or robust tumor-immune infiltration with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional

imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010).Therefore, mandatory tumor biopsies must be collected at the first evidence of radiographic disease recurrence, if clinically feasible.

A tumor biopsy performed in patients at the time of first evidence of radiographic recurrence will be used to evaluate whether the radiographic findings are consistent with the presence of tumor or if the appearance of recurrence was caused by tumor immune infiltration. In addition, mechanisms related to tumor recurrence or occurrence, resistance, prognostic, and pharmacodynamic relationships in tumor biomarkers (including but not limited to TIGIT, PD-L1, CD8, macrophage markers, mutation status, and others) as well as to efficacy in the adjuvant treatment setting may be evaluated. DNA and/or RNA extractions may be performed to enable the identification of somatic mutations by NGS to contribute to an improved understanding of the dynamics of PD-L1 expression, tumor immunobiology, and the relationship to disease recurrence and DFS in the adjuvant setting.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The following dosing regimen is recommended for tiragolumab when administered in combination with atezolizumab for resected Stage IIB, IIA, or select IIB, PD-L1≥1% TC participants with NSCLC who have received adjuvant platinum-based chemotherapy.

- Tiragolumab 840 mg co-infused with atezolizumab 1680 mg every four weeks (Q4W)

The rationale for the 840 mg Q4W regimen of tiragolumab was based on the Phase I Study GO30103 (unpublished data), which tested the safety and PK of escalating tiragolumab doses from 2−1200 mg every three weeks (Q3W) as a monotherapy or in combination with 1200 mg Q3W atezolizumab, in addition to an 840 mg regimen in combination with 1680 mg of atezolizumab Q4W co-infused or administered sequentially in participants with locally advanced or metastatic solid tumor malignancies.

In Study GO30103, the MTD of tiragolumab as a single agent or in combination with atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose. Linear pharmacokinetics were observed at doses of 100 mg IV or greater in combination with atezolizumab Q3W. Complete occupancy of peripheral TIGIT receptors on CD4+ T cells, CD8+ T cells, and NK cells was observed beginning at the 30 mg Q3W dose of tiragolumab and remained sustained at all higher doses. Anti-tumor activity was observed across doses of tiragolumab beginning at 30 mg in combination with 1200 mg of atezolizumab Q3W with prolonged stable disease observed in participants beginning at tiragolumab 400 mg IV Q3W in combination with atezolizumab. Anti-tumor activity was further observed using 840 mg of tiragolumab in combination with 1680 mg atezolizumab Q4W.

Based on receptor occupancy in the periphery, saturation of TIGIT is expected with the 840 mg Q4W (600 mg Q3W equivalent) regimen of tiragolumab. The dose proportionality assessment findings in Study GO30103 are consistent with saturating peripheral receptor occupancy at dose levels $\geq$100 mg, which are expected to overcome the target mediated drug disposition effect leading to linear pharmacokinetics and is consistent with maintaining C_{min} ~$\geq$10 μg/mL in the overwhelming majority of participants. Given the expectations for variability in drug exposure and uncertainty in binding rates, tumor vascularization, and target expression in tumor tissue relative to peripheral blood, the 840 mg Q4W (600 mg Q3W equivalent) regimen of tiragolumab is expected to be a conservative dose level to ensure adequate binding. This regimen is also associated with a low anti-drug antibody (ADA) incidence, with 0% and $<$3% of participants developing ADAs to tiragolumab for the 840 mg Q4W regimen in combination with atezolizumab, or for tiragolumab (doses of 2−1200 mg Q3W) in combination with atezolizumab, respectively.

Preliminary analysis of available data from tiragolumab dose levels using a Q3W dosing frequency, including 1200 mg Q3W (the maximum assessed tiragolumab dose in the Phase I Study GO30103), in addition to the 840 mg Q4W cohort data, demonstrated that there was not a clinically meaningful exposure-safety relationship. Further, simulations based on the population PK model of tiragolumab showed that the 840 mg Q4W dosing regimens achieved generally comparable exposure to 600 mg Q3W and were within the range of observed exposures from the 1200 mg Q3W dose levels.

The 840 mg Q4W dose and schedule of tiragolumab or 600 mg Q3W equivalent has also been adopted by multiple studies, including Phase III registrational studies, across the tiragolumab development program in multiple indications, including, but not limited to, hepatocellular carcinoma (HCC), NSCLC, small cell lung cancer, cervical cancer, and head and neck squamous cell carcinoma.

Study GO30103 data further demonstrated that Q4W co-infusion of 840 mg tiragolumab with 1680 mg atezolizumab provided similar pharmacokinetics and safety profiles as those from the sequential administrations. Overall, 840 mg of tiragolumab co-infused with atezolizumab in a Q4W regimen was well managed. The 840 mg IV Q4W regimen of tiragolumab further aligns with the 1680 mg IV Q4W regimen for atezolizumab which is an approved regimen for atezolizumab in both monotherapy and combination therapy settings (Tecentriq USPI).

4.4 END OF STUDY DEFINITION

The end of study will occur when the last patient, last visit has occurred or the date at which the last data point required for statistical analysis (i.e., final analysis for DFS), whichever occurs later. The total length of study, from randomization of the first participant to the end of study, is expected to be approximately 15 years. In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

Participation will continue until withdrawal or death due to any cause.

5. STUDY POPULATION

Approximately 1150 (700 participants with PD-L1 ≥ 50% TC and 450 participants with PD-L1 1%–49% TC by the investigational VENTANA PD-L1 (SP263) CDx assay) participants with completely resected Stage IIB, IIIA, and select IIIB (T3N2) NSCLC who have received adjuvant platinum-based doublet chemotherapy will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Histological or cytological diagnosis of Stage IIB, IIIA, and select IIIB (T3N2) NSCLC (per the UICC/AJCC staging system, 8th edition; Detterbeck at al. 2017) of either non-squamous or squamous histology
  - Participants with tumors of mixed NSCLC histology must be classified as being non-squamous or squamous on the basis of the major histologic component
  - Participants with tumors of mixed histology containing both NSCLC and small-cell lung cancer are not eligible
  - NSCLC with histology of large cell neuroendocrine carcinoma, sarcomatoid carcinoma, or NSCLC not otherwise specified are not eligible
- Participants must have had complete resection of NSCLC (no residual tumor and all surgical margins negative for invasive carcinoma)
  - Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.
  - Participants who have had only segmentectomies or wedge resections are not eligible for this study.
- At a minimum, mediastinal lymph node systematic sampling will have occurred, though complete mediastinal lymph node dissection (MLND) is preferred. Systematic sampling is defined as removal of at least one representative lymph node at specified stations. MLND entails resection of all lymph nodes at those same stations. Sampling or MLND at a minimum of 2 lymph node N2 stations is required. Exceptions will apply for the following situations:

- If mediastinoscopy or EBUS was performed preoperatively, diagnostic mediastinal lymph node sampling can be used to meet the minimum of 2 lymph node N2 stations.
- If there is clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node stations, the participant will be considered eligible if no lymph nodes are found in those stations.

- Participants must have received between one to four cycles (four preferred) of adjuvant histology-based platinum doublet chemotherapy: cisplatin (preferred) or carboplatin, with pemetrexed (non-squamous), gemcitabine, docetaxel, vinorelbine, etoposide, or paclitaxel. Refer to NCCN/ESMO guidelines for acceptable adjuvant chemotherapy regimens (see Appendix 12)
- Participants must have recovered adequately from surgery and from adjuvant chemotherapy (no Grade >2 unresolved toxicity)
  - Patients with an irreversible toxicity that is managed and is not expected to be exacerbated by study drug treatment may be included (e.g., hearing loss)
- Patients must begin adjuvant chemotherapy within 12 weeks of their surgery date
- Patients must be randomized no more than 70 days (10 weeks) from last dose of chemotherapy (Day 1 of last cycle)
- Tumor PD-L1 expression with a $\geq 1\%$ TC as determined by the investigational VENTANA PD-L1 (SP263) CDx Assay, documented through central testing of a representative tumor tissue specimen
  - A representative formalin-fixed, paraffin-embedded (FFPE) existing resected tumor specimen in a paraffin block (preferred) or at least 15-20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If central testing for *EGFR* mutations and/or *ALK* translocations are required, an additional five unstained slides must be provided. Tumor tissue should be of good quality based on total and viable tumor content (i.e., preserved cellular context and tissue architecture).
  - For mainland China participants, slides will be collected in compliance with Human Genetic Resources Administration of China approval.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - ANC $\geq 1.5 \times 10^9$/L ($\geq 1500/\mu$L) without granulocyte colony-stimulating factor support, with one exception: Participants with benign ethnic neutropenia (BEN): ANC $\geq 1.3 \times 10^9$/L ($\geq 1300/\mu$L) are eligible

    BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019).

BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups

- Lymphocyte count $\geq 0.5 \times 10^9$/L ($\geq$500/μL)
- Platelet count $\geq 100 \times 10^9$/L ($\geq$100,000/μL) without transfusion
- Hemoglobin $\geq$ 90 g/L ($\geq$ 9 g/dL)

  Participants may be transfused to meet this criterion.
- AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN)
- Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

  Participants with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN
- Creatinine clearance $\geq$ 30 mL/min (calculated by institutional standards or through use of the Cockcroft-Gault formula)
- Albumin $\geq$ 25 g/L ($\geq$2.5 g/dL)
- For participants not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN

- For participants receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening, with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq$200/μL, and have an undetectable viral load.
- Participants meeting one of the following criteria for hepatitis B virus (HBV)
  - Negative hepatitis B surface antigen (HBsAg) test at screening, accompanied by either of the following:

    Positive hepatitis B surface antibody (HBsAb)

    Negative HBsAb and negative total hepatitis B core antibody (HBcAb)
  - HBV DNA $<$ 500 IU/mL at screening for participants with positive total HBcAb test and negative HBsAb test

    Participants with detectable HBV DNA should be managed per institutional guidelines.
  - Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

    The HCV RNA test must be performed for participants who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period, for 90 days after the final dose of tiragolumab/placebo and for 5 months after the final dose of atezolizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of

amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab/placebo to avoid exposing the embryo. Male participants must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Any history of prior NSCLC within the last 5 years
- Previous NSCLC must have been treated with surgery only
- Any evidence of residual disease or disease recurrence following surgical resection of NSCLC, or during or following adjuvant chemotherapy
- NSCLC known to have mutation in the *EGFR* gene or an *ALK* fusion oncogene:
  - Participants with non-squamous NSCLC who have an unknown *EGFR* or *ALK* status will be required to be tested at pre-screening or screening.

- Participants with squamous NSCLC who have an unknown EGFR or ALK status are eligible and will not be required to be tested at pre-screening or screening.
- EGFR and/or ALK status may be assessed locally or at a central laboratory.

  EGFR and/or ALK status assessed locally must be performed on tissue using a validated health authority–approved or an appropriately validated NGS test performed in a Clinical Laboratory Improvement Amendments (CLIA) or equivalently certified laboratory. EGFR test must detect mutations in exons 18–21.

  If samples are submitted for central EGFR and/or ALK testing, an additional five slides must be provided.

- Prior treatment with systemic therapy (e.g., chemotherapy or immunotherapy) for the treatment of NSCLC, with the exception of adjuvant platinum-based chemotherapy as outlined in the inclusion criteria
- Prior treatment with radiation therapy for NSCLC (including PORT), with the exception of localized symptom-directed radiation prior to surgical resection
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 11 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Participants with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
  - Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
  - Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of the following conditions are met:

    Rash must cover $<$10% of body surface area.

    Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

    There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- Positive Epstein-Barr virus (EBV) viral capsid antigen IgM test at screening

  - An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Participants with a positive EBV PCR test are excluded.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study treatment period
- History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$ 90%) such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could impact participant safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Participants receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine, during study treatment, for 90 days after the final dose of tiragolumab/placebo, and for 5 months after the final dose of atezolizumab
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti-TIGIT, anti–PD-L1, and anti–PD-1 therapeutic antibodies

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Participants who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  - Participants who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment, within 90 days of the last dose dose of tiragolumab/placebo or within 5 months after the final dose of atezolizumab
  - Women of childbearing potential must have a negative pregnancy test result within 14 days prior to randomization.
- Any condition that, in the opinion of the investigator, would interfere with the participant's safe participation in and completion of the study, the evaluation of the study drug, or the interpretation of participant safety or study results.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion as long as the time between last dose of chemotherapy and randomization does not exceed 70 days (10 weeks). The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMP) for this study are tiragolumab, tiragolumab placebo, and atezolizumab (see Appendix 10).

6.1 STUDY TREATMENT ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Tiragolumab	Tiragolumab Placebo	Atezolizumab
Use	Experimental	Placebo	Experimental
Type of medicinal product	IMP	IMP	IMP
Drug form	liquid concentrate	liquid	liquid concentrate
Unit dose strengths	600 mg/10 mL	Not applicable	1200 mg/20 mL or 840 mg/14 mL
Dosage levels	840 mg Q4W	0 mg	1680 mg Q4W
Formulations	Refer to pharmacy manual		
Packaging	15 mL glass vials	15 mL glass vials	20 mL glass vial or 15 mL glass vial
Labeling	Per local regulations		
Route of administration	IV infusion		
Source	Sponsor		

IMP = investigational medicinal product; Q4W = every 4 weeks

The treatment regimens are summarized in Section 4.3. In this protocol, "study treatment" refers to the combination of treatments assigned to participants as part of this study (i.e., atezolizumab plus tiragolumab).

Administration of study treatment will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Section A4–5.

6.1.1 Tiragolumab and Atezolizumab or Placebo and Atezolizumab Co-infusion

Tiragolumab or placebo will be administered by IV infusion at a fixed dose of 840 mg together with 1680 mg of atezolizumab mixed in the same IV bag for co-infusion on Day 1 of each 28-day cycle. Tiragolumab/atezolizumab and placebo/atezolizumab co-infusions will be administered per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Infusions of Atezolizumab Mixed with Tiragolumab/Placebo

First Infusion	Subsequent Infusions
• No premedication is allowed for the first infusion of tiragolumab/placebo and atezolizumab in the same IV infusion bag. • Record the participant's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within 60 minutes prior to starting the infusion • Deliver the initial dose over 90 (±10) minutes • If clinically indicated, record the participant's vital signs every 15 (±5) minutes during the infusion	• Record the participant's vital signs within 60 minutes prior to starting the infusion • If the last infusion was well tolerated without an IRR, the delivery time for the next infusion may be reduced by 30 minutes, provided the infusion time remains no less than 30 minutes. • If a participant experiences an IRR or hypersensitivity reaction during the first or any subsequent infusion, an antihistamine and/or antipyretic medications may be administered for subsequent infusions at the discretion of the investigator. The duration of the next infusion should not be less than the duration of the last infusion if IRR occurred in the last infusion. • Record vital signs every 15 (±5) minutes during the infusion if clinically indicated

Observation Period after First Infusion	Observation Period after Subsequent Infusions
• After the infusion, the participant begins a 60-minute observation period. • Record the participant's vital signs at 30 (±10) minutes after the end of the infusion • Participants should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the participant tolerated the last and current infusion well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the participant experienced an IRR during the last or current infusion, the observation period should be 60 minutes. • If clinically indicated, record the participant's vital signs at 30 (±10) minutes after the end of the infusion.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs are provided in A4–5.3.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or Atezolizumab and Tiragolumab Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Randomization must be completed within 70 days (10 weeks) after the final dose of chemotherapy. Eligible participants will be randomized in a 1:1 ratio to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab. Participants should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days of randomization.

Eligible participants will be stratified by tumor histology (squamous vs. non-squamous), disease stage (Stage II vs. Stage IIIA + select IIIB [T3N2]), and PD-L1 status (1%–49% TC vs. ≥ 50% TC) by the investigational VENTANA PD-L1 (SP263) CDx assay. A permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm within levels of the stratification factors.

6.3.2 Blinding

Study site personnel and participants will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. PK and ADA samples from participants assigned to the comparator arm will not be analyzed for triagoluamb PK and ADA except by request (e.g., to evaluate a possible error in dosing or ADA in-study cut point assessment).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is deciding whether a patient should initiate subsequent treatment with a health authority-approved therapy for that indication. However, unblinding will not be permitted if an investigator is deciding whether to initiate subsequent treatment with an unproven therapy for that indication.

The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to a drug listed in Section 8.3.4. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision.

Appendix 3Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the tiragolumab/placebo and atezolizumab dose is not permitted in this study. Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Section A4–5.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide atezolizumab, tiragolumab or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab or tiragolumab in accordance with the Roche Global Policy on Continued Access to IMP, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until participant status returns to the pre-overdose status.

6.8 CONCOMITANT THERAPY

Any medication (e.g. prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation/completion visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

Participants are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of < 1% per year (see Section 5.1)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID 19)

  Live, attenuated vaccines are not permitted (see Section 6.8.3)

- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent infusions, at the discretion of the investigator.

In general, investigators should manage a participant's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 6.8.2 and Section 6.8.3) as clinically indicated, per local standard practice. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

6.8.2 Cautionary Therapy

6.8.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with tiragolumab and/or atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with tiragolumab and/or atezolizumab therapy.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.3) may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, RT, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease recurrence is documented and the participant has discontinued study treatment.
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during study treatment, for 90 days after the final dose of tiragolumab/placebo, and for 5 months after the final dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with study treatment

6.9 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Intolerable toxicity related to atezolizumab or tiragolumab/placebo, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the participant's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Confirmed disease recurrence per investigator assessment after an integrated assessment of radiographic data and biopsy sample results (if available)

– For equivocal findings of recurrence (e.g., very small or uncertain new lesions or lymph nodes), treatment may be continued until the next scheduled assessment.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants may complete the treatment discontinuation/completion visit at the time of the last dose or confirmed disease recurrence or return to the clinic no more than 30 days after the final dose of study treatment for a treatment discontinuation/completion visit.

Participants who discontinue study treatment (for any reason) in the absence of confirmed disease recurrence will continue to undergo disease status assessments as outlined in the schedule of activities (see Section 1.3).

7.2 POST-TREATMENT ASSESSMENTS

After treatment discontinuation/completion, paitents will continue to be followed in the post-treatment period, which includes disease status assessments, PROs, and survival follow-up (see Table 1 Schedule of Activities).

Information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the participant withdraws consent or the Sponsor terminates the study). Information on subsequent anti-cancer therapies will include systemic therapies (e.g., chemotherapy, targeted therapy, CIT), surgery (e.g., resection of disease), and radiation procedures (e.g., RT to a tumor lesion).

7.3 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Partial withdrawl of consent is permitted. After treatment discontinuation or completion, a participant may withdraw from a subset of assessments. It should be documented in both the medical records and the eCRF which information the participant agreed to continue despite the participant's partial withdrawal of informed consent.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Signing of the ICFs must occur within 60 days of randomization. Participants have the option to sign the Pre-Screening ICF to consent to PD-L1 tissue testing and/or *EGFR* or *ALK* testing (as applicable) prior to signing the main ICF for all screening procedures and study participation. Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including NSCLC history and other conditions, prior cancer therapies and procedures), reproductive status, smoking history will be recorded at screening. Any medication and vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable.

8.1 EFFICACY ASSESSMENTS

8.1.1 Radiographic Assessments for Disease Status Evaluation

Screening and subsequent disease assessments must include CT scans with contrast of the chest and abdomen (including liver and adrenal glands). If a CT scan with contrast is contraindicated (e.g., in participants with impaired renal clearance), a non-contrast CT of the chest plus an magnetic resonance imaging (MRI) of the abdomen is preferred, and a chest/abdomen CT non-contrast is acceptable. MRI scan (preferred) or contrast CT of the brain must be done at screening to evaluate CNS metastasis in all participants (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

The same radiographic modality (e.g. CT with contrast) and procedures (e.g., the same contrast protocol for CT scans) used at screening should be used for subsequent disease assessments.

The use of radiopharmaceutical products (e.g., 18F-FDG, Tc-99m, MIBG) and contrast agents (e.g., gadolinium-based or iodinated contrast media) in study imaging assessments will be consistent with standard/local practice, and will not involve a route of administration, dose, participant population, or any other factor that significantly increases the risk (or decreases the acceptability of the risk) to participants. The products employed in these procedures will be at the discretion of participating investigators, and shall be locally authorized or otherwise used in compliance with local regulations. The results of this study will not be used to support any new indication or change in labeling for these products.

All participants will undergo disease assessments at screening and every 16 weeks ($\pm$14 days) starting at Cycle 1, Day 1 in the first year, every 26 weeks ($\pm$ 4 weeks) during Years 2–5 and annually thereafter (low dose non-contrast CT recommended after 5 years). Disease assessments will continue per schedule regardless of whether study treatment is held, discontinued, or completed until disease recurrence, withdrawal of consent, death, of study termination by Sponsor, whichever occurs first. At the investigator's discretion, disease assessments may be repeated at any time if disease recurrence is suspected.

Disease recurrence must be determined radiographically as evidenced by local/regional recurrence, distant metastasis, or a second primary NSCLC. If a disease assessment shows disease recurrence, it must be confirmed pathologically, unless not clinically feasible. If a biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the participant may continue with scheduled study treatment. If a biopsy for disease recurrence confirmation is performed, any leftover biopsy tissue is strongly encouraged to be submitted for exploratory biomarker research (optional consent required for exploratory research; see Section 8.10 for details).

If a disease assessment shows equivocal findings (e.g., mediastinal nodes measuring $<$1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring $<$ 1 cm in the longest diameter), a biopsy must be performed. If a biopsy is not feasible or safe, then confirmatory scans must be performed no later than the next scheduled assessment, or earlier if clinically indicated. If the confirmatory scan shows unequivocal radiographic disease recurrence, the date of disease recurrence is the date of the first assessment of recurrence.

If disease recurrence is suspected prior to treatment discontinuation/completion, administration of study treatment will continue between the initial assessment of recurrence and confirmation of disease recurrence.

Radiographic images will be submitted to an IRF for a quality and completeness check, for potential blinded independent central review (BICR), and for temporary storage prior to transferring images to the Sponsor for the long term retention.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.2 Clinical Outcome Assessments

Patient-reported outcome instruments will be completed to assess the participant-reported tolerability of tiragolumab plus atezolizumab at the selected dosages, and to confirm the safety profile of the doublet combination. In addition, PRO instruments will enable the capture of each participant's direct experience with tiragolimab plus atezolizumab.

PRO data will be collected through use of the following instruments: EORTC QLQ-C30, EORTC QLQ-LC13, EORTC-IL46, PRO-CTCAE (selected items), and EQ-5D-5L Appendix 6).

The PROs should be administered in the following order: EORTC QLQ-C30, EORTC QLQ-LC13, EORTC-IL46, PRO-CTCAE (selected items), and EQ-5D-5L. The PRO--CTCAE and EORTC IL46 are described in Section 8.2.6, and the EQ-5D-5L in Section 8.9.1.

8.1.2.1 EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Section A6–1.1). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (Fatigue, Nausea and Vomiting, and Pain), global health status (GHS) and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

8.1.2.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 is a self-reported PRO measure that is a lung cancer-specific module to the EORTC QLQ-C30 (Bergman et al. 1994) (see Section A6–1.2). It is composed of 13 items that assess lung cancer-associated symptoms. The lung cancer module includes one multi-item scale to assess dyspnea, and a series of single items

assessing pain in different areas, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The QLQ-LC13 has a recall period of 7 days. All 13 items are scored on a 4-point scale that ranges from “not at all” to “very much”. The QLQ-LC13 takes approximately 5 minutes to complete.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

8.2.3 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each participant should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.2.6 Clinical Outcome Assessments

PRO instruments will enable the capture of each participant's direct experience with tiragolumab and atezolizumab. Participant-reported tolerability will be assessed with the PRO-CTCAE and EORTC IL46.

The EORTC QLQ-C30 and EORTC QLQ-LC13 are described in Section 8.1.2, and the EQ-5D-5L is described in Section 8.9.1.

8.2.6.1 PRO-CTCAE

The PRO-CTCAE is a validated item library that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 participant-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of 17 symptoms deemed most applicable to the current study treatments has been selected for this study (see Section A6–1.4). Symptoms have been selected on the basis of data from earlier-phase studies for tiragolumab and known side effects of atezolizumab and/or tiragolumab.

8.2.6.2 EORTC IL46

The EORTC IL46 (see Section A6–1.3) is a validated single item from the EORTC Item Library which assesses the extent that participants have been troubled by the side effects from their treatment. It is rated on a 4-point scale, ranging from “not at all” to “very much”.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment/study (see Section 6.9).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 30 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3), or until initiation of new systemic anti-cancer therapy, whichever occurs first. All serious adverse events will be collected and followed until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of subsequent anti-cancer therapy.

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been

discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Tiragolumab	Tiragolumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.4.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

8.3.4.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 8.3.4.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study, within 90 days after the final dose of tiragolumab/placebo, and within 5 months after the final dose of atezolizumab.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab/placebo.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Death Events

Information on reporting deaths is provided in Appendix 3 .

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

8.3.8.1 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Serum samples will be collected for measurement of serum concentrations of atezolizumab and tiragolumab according to the schedule outlined in Section 1.3 (Table 2). Serum samples for PK analysis will be tested by the Sponsor or Sponsor's designee for analysis by validated assay.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of atezolizumab and tiragolumab. Samples collected for analyses of tiragolumab and atezolizumab, serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study Report has been completed at a facility selected by the Sponsor to enable further analysis of pharmacokinetics to atezolizumab and tiragolumab or associated methods.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

Refer to Section 8.7 and Appendix 9 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Tumor tissue sample obtained for determination of PD-L1 expression for determining eligibility and for participant stratification purposes and for exploratory research on biomarkers including biomarker assay development

  A representative formalin-fixed, FFPE existing resected tumor specimen in a paraffin block (preferred) or at least 15-20 or more slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.

  Tumor tissue should be of good quality, as determined on the basis of total and viable tumor content. Samples must preserve tissue architecture and preserve cellular context.

Analysis of PD-L1 expression will be performed using the investigational VENTANA PD-L1 (SP263) CDx Assay. Additional information about the use of this assay can be found in the clinical performance study protocol.

- Blood, plasma, serum, and/or tissue samples will be used for exploratory research on biomarkers including biomarker assay development
- Tumor tissue sample obtained at the time of recurrence, if deemed clinically feasible, for exploratory research on biomarkers

  Patients will undergo a mandatory tumor biopsy to obtain a tumor sample, unless not clinically feasible, at the time of radiographic disease recurrence. Biopsies at the time of recurrence should be performed within 40 days after the first evidence of recurrence or prior to the next anti-cancer therapy, whichever is sooner.

  Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are acceptable.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.1.

Exploratory biomarker research may include, but will not be limited to, analysis of circulating tumor DNA (ctDNA), genes or gene signatures associated with tumor immunobiology (such as *KRAS*, *PTEN*), lymphocytes, and cytokines associated with T cell activation. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling.

Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, with a focus on somatic variants. WGS or WES of blood samples with a focus on germline variants may also be conducted, but only at participating sites (see Section 8.10.1).

Next-generation sequencing (NGS) may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If permitted by local law, the investigator may share and discuss the results with the participant, unless the participant chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. The report may be included in the participant's medical record. Results will not be available for samples that do not meet criteria for testing.

After PK or immunogenicity analyses have been completed, any remaining serum may be used for exploratory biomarker research described above.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 2). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her remaining samples to be stored for optional exploratory research (see Section 8.10), biomarker samples will be destroyed no later than 10 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to atezolizumab and tiragolumab will be evaluated in serum samples collected according to the schedule of activities (Table 2).

Serum samples will be screened for antibodies binding to atezolizumab and tiragolumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to atezolizumab and tiragolumab and/or further characterize the immunogenicity of atezolizumab and tiragolumab.

The detection and characterization of antibodies to atezolizumab and tiragolumab will be performed through use of a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study Report has been completed at a facility selected by the Sponsor to enable further analysis of immunogenicity of atezolizumab and tiragolumab .

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

8.9.1 EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Section A6–1.5). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state.

The EQ-5D-5L is designed to capture a participant's current health status. Published weighting systems allow for creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters. The data collected will include the reasons and duration of hospitalizations and emergency room visits and exclude procedures, tests, and encounters mandated by the protocol.

The Sponsor may use the collected data to conduct economic analyses.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing with a Focus on Germline Variants (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify germline variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants..

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.10.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

Sites that opt out of RBR participation can ignore this section.

Use and storage of RBR samples (which may include remaining samples and/or samples collected specifically for the RBR) is summarized below:

Who can use the samples?	The study team/program has use of the samples and can decide if and when other researchers can use the samples.
When are the samples available for analysis?	Samples can be analyzed any time during or after the study, until the samples are used up or no longer needed (or as outlined in the locally approved version of the RBR ICF).
What type of research is allowed?	The samples can be used for study-specific research or for extended research as outlined in the RBR section of the ICF.
Who manages the samples?	Samples are managed by the Pharma Biosample Services (PBS) group. PBS also offers sample processing services (such as DNA extraction, RNA preparation, plasma/serum aliquoting).

Where are the samples stored?	During the study, samples are usually managed by a central laboratory. No later than the time of study closure, samples are transferred to one of a group of storage facilities under the oversight of Roche and managed by PBS. Study teams can request that samples be transferred to a PBS-managed storage facility prior to study closure (e.g., to allow for sample processing by PBS).

8.10.3 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.4 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.4) will not be applicable at that site.

8.10.5 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab and/or tiragolumab, diseases, or drug safety:

- Tumor tissue samples collected at screening and at disease progression

- Any remaining blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.6 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email

address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.7 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.8 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the

site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.9 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypotheses will be formally tested regarding the effect of tiragolumab plus atezolizumab compared to placebo plus atezolizumab on investigator-assessed disease free survival (DFS) in the PD-L1 high analysis set (PHAS) (PD-L1 $\geq$50% TC by SP263) and full analysis set (FAS) (PD-L1 $\geq$ 1% TC by SP263).

The null (H_0) and alternative (H_1) hypotheses regarding investigator-assessed DFS in the PHAS and FAS will be tested at a two-sided significance level of 0.038 and 0.012, respectively, and can be phrased in terms of the population hazard ratio λ between the experimental arm and the control arm:

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

All hypothesis tests will be two-sided unless stated otherwise.

9.1.1 Sample Size Determination

A total of approximately 1150 participants (approximately 700 participants with PD-L1 $\geq$ 50% TC and approximately 450 participants with PD-L1 1%–49% TC by investigational VENTANA PD-L1 (SP263) CDx assay) will be randomized into the study. The detailed assumptions and calculations are listed below.

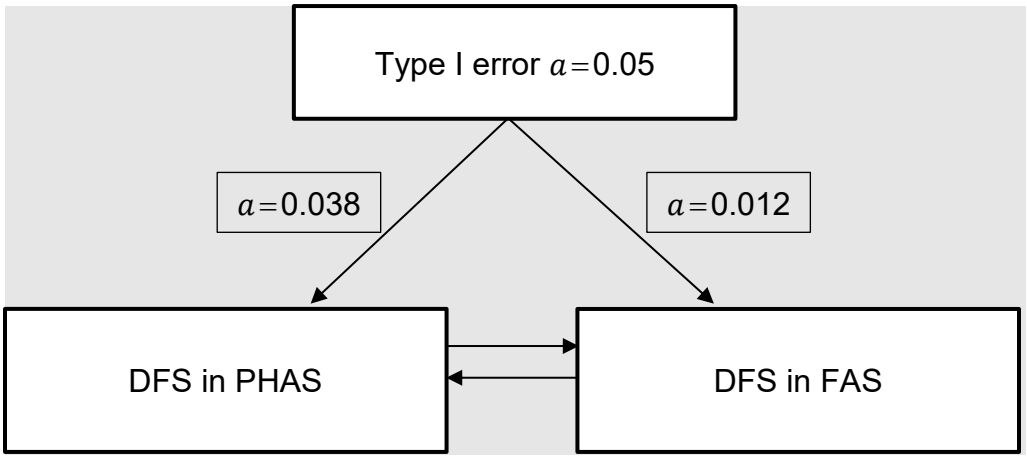
9.1.1.1 Type I Error Control

The overall type I error rate for the study is 0.05 (two-sided). The primary endpoints of investigator-assessed DFS in PHAS and FAS will be tested at a two-sided α level of 0.038 and 0.012, respectively (see Figure 2).

- If DFS is statistically significant in the PHAS, then the two-sided α of 0.038 will be recycled to the FAS to be tested at a two-sided α of 0.05.
- If DFS is statistically significant in the FAS, then the two-sided α of 0.012 will be recycled to the PHAS to be tested at a two-sided α of 0.05.

The study is positive as long as any of the primary endpoints is positive.

Figure 2 Type I Error Control Plan



DFS = Disease-free survival; FAS = full analysis set; PHAS = PD-L1 ≥ 50% TC analysis set.

9.1.1.2 Investigator-Assessed Disease-Free Survival

The final analysis for the primary endpoint of investigator-assessed DFS will take place when approximately 322 DFS events in the PHAS and approximately 652 DFS events in the FAS have been observed, whichever occurs later.

The estimated number of events required to demonstrate efficacy with regard to DFS in the PHAS are based on the following assumptions:

- 1:1 randomization ratio
- Two-sided α of 0.038
- DFS curve follows the exponential distribution
- Median DFS of 65 months for placebo plus atezolizumab arm
- 85% power to detect a DFS HR of 0.70
- One interim analysis will be performed when approximately 249 DFS events in the PHAS have occurred. The stopping boundaries are computed using the Generalized Haybittle-Peto boundaries (Haybittle 1971) with unequal p-values of

0.0260 and 0.0252 at the interim and final DFS analysis, respectively. (Refer to Section 9.4 for details of the planned interim analysis.)

- Enrollment period of approximately 64 months
- Annual drop-out rate of 5%

The estimated number of events required to demonstrate efficacy with regard to DFS in the FAS are based on the following assumptions:

- 1:1 randomization ratio
- Two-sided α of 0.012
- DFS curve follows the exponential distribution
- Median DFS of 51 months for placebo plus atezolizumab arm
- 74% power to detect a DFS HR of 0.78
- One interim analysis will be performed when approximately 539 DFS events in the FAS have occurred. The stopping boundaries are computed using the Generalized Haybittle-Peto boundaries (Haybittle 1971) with unequal p-values of 0.0090 and 0.0071 at the interim and final DFS analysis, respectively. (Refer to Section 9.4 for details of the planned interim analysis).
- Enrollment period of approximately 64 months
- Annual drop-out rate of 5%

With these assumptions, the final DFS analysis will take place approximately 120 months after the first participant is randomized. The minimum detectable difference in DFS HR at the final analysis is approximately 0.78 for the PHAS and 0.81 for the FAS.

9.2 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 7.

Table 7 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
PHAS	All randomized participants with PD-L1 $\geq$ 50% TC by the investigational VENTANA PD-L1 (SP263) CDx assay; will be included in the analyses according to the treatment to which they were assigned.
SAS	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
Atezolizumab PK Analysis Set	All participants who received any dose of atezolizumab with at least 1 post-baseline atezolizumab PK assessment available
Tiragolumab PK Analysis Set	All participants who received any dose of tiragolumab with at least 1 post-baseline tiragolumab PK assessment 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 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 sample.

ADA = ant-drug antibody; FAS = full analysis set; PHAS = PD-L1 high analysis set; PK = pharmacokinetic; SAS = safety analysis set

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be finalized prior to the interim efficacy analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The analyses specified in the Statistical Analysis Plan supersede those specified here.

9.3.1 General Considerations

All efficacy analyses will be performed on the PHAS and FAS, unless otherwise specified. The treatment policy will be used for the intercurrent events of both early discontinuation from the study treatment and starting of non-protocol anti-cancer therapy prior to the event of interest.

All safety analyses will be performed on the SAS, unless otherwise specified.

9.3.2 Estimation Methods for the Primary Estimands

The primary objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in participants with resected, Stage IIB, IIIA, or select IIIB (T3N2 only) (AJCC 8th edition) PD-L1 $\geq$ 50% TC and PD-L1 $\geq$ 1% TC NSCLC who have received adjuvant platinum-based chemotherapy. The primary endpoints are investigator-assessed DFS in the PHAS and FAS.

Investigator-assessed DFS is defined as the time from randomization to the occurrence of local/regional or distant recurrence of NSCLC, new primary NSCLC, or death from any cause (whichever occurs first), as determined by the investigator. The corresponding estimands are as described in Section 3. Data for participants who have not experienced local/regional or distant recurrence of NSCLC, a new primary NSCLC, or death will be censored at the date of the last tumor assessment. If no post-baseline data are available, DFS will be censored at the date of randomization.

The stratified log-rank test will be used to compare DFS between the two treatment arms. The HR for DFS will be estimated using a stratified Cox regression model, along with the 95% CI. Stratification factors for analysis in FAS will include histology (non-squamous vs. squamous), stage of disease (Stage IIB vs. Stage IIIA + select IIIB [T3N2]) and PD-L1 status (1%–49% TC vs. $\geq$ 50% TC). Stratification factors for analysis in PHAS will include histology and stage of disease. Results of the unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median

DFS for each treatment arm, and the Kaplan-Meier curve will be constructed to provide a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the two-sided 95% CI for the median DFS for each treatment arm.

The type I error control plan is presented in Section 9.1.1.1. Further analysis details including sensitivity/supplementary analyses of the primary endpointswill be specified in the SAP.

9.3.3 Estimation Methods for the Secondary Endpoints

9.3.3.1 Overall Survival

Overall survival after randomization is defined as the time from randomization to death from any cause. Data for participants who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization.

The methodology for comparing OS between treatment arms in PHAS and FAS will be the same as the method used for treatment comparison for the primary endpoints of investigator-assessed DFS.

Overall survival will be analyzed at the time of the DFS analyses.

9.3.3.2 Investigator-Assessed Disease-Free Survival Rate at 3-Year 5-Year and 7-Year

The investigator-assessed DFS rate at 3 years, 5 years and 7 years will be analyzed by treatment arm. The DFS rates will be estimated by the Kaplan-Meier methodology for each treatment arm, with two-sided 95% CIs calculated using Greenwood's formula.

9.3.3.3 Clinical Outcome Assessment Analysis

The proportion of participants who maintained or meaningfully improved from baseline in patient-reported role, emotional, and physical functioning and GHS/QoL as measured by the EORTC QLQ-C30 will be summarized by treatment arm. In general, a change of 10 points or more on scales of the EORTC QLQ-C30 was established by Osoba et al. (1998) to be clinically meaningful. This has been largely confirmed in studies with lung cancer patients, and specific estimates for individual scales of the EORTC QLQ-C30 and LC13 in lung cancer will be applied (Coon et al. 2022; Musoro et al. 2023). Maintenance of baseline is defined as a less than 10-point increase or decrease in deterioration of these domains. Details will be provided in the SAP.

9.3.3.4 Safety Analyses

Safety analyses will be conducted in the SAS, defined as participants who receive at least one dose of tiragolumab/placebo or atezolizumab (see Section 9.2). Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. Cytokine release syndrome (CRS) will also be graded according to the ASTCT CRS Consensus Grading Scale. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur or worsen on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.3.4 Exploratory Analyses

9.3.4.1 Clinical Outcome Assessment Analyses

The analysis population for the EORTC QLQ-C30, and QLQ-LC13 is the FAS. Completion rates will be summarized at each timepoint by treatment arm for the EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L using the FAS.

Summary statistics (mean, SD, 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. The number and proportion of participants who improved, worsened, or remained stable on each of the scales of the EORTC QLQ-C30 and QLQ-LC13 will be summarized at each visit by treatment arm. Comparisons between treatment groups will be made.

The analysis population for the PRO-CTCAE and EORTC IL46 is the SAS. Summaries of the data over time will be based on the number of participants who provided data at each time point. Completion rates will be summarized at each timepoint by treatment arm for the PRO-CTCAE and EORTC IL46.

Results from these analyses will be presented separately from the safety analyses.

For patient-reported tolerability, the PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic AE occurrence over the course of the study. PRO-CTCAE data will be analyzed at the item level in accordance with current NCI recommendations for data handling (Basch et al., 2014). The number

(percentage) of participants reporting symptoms by frequency, severity, and interference will be reported at each visit by treatment arm. The change in the frequency of responses from baseline for each symptom will also be summarized at each visit by treatment arm.

Patient-reported bother with side effects, as measured by the EORTC IL46 item, will be summarized descriptively at each assessment timepoint. The number (percentage) of participants reporting bother will be reported at each visit by treatment arm. The change in the frequency of responses from baseline will also be summarized at each visit by treatment arm.

Additional analyses for the PROs are described in the SAP.

9.3.4.2 Subgroup Efficacy Analyses

The effects of demographics (e.g., age, sex, race/ethinicity) and baseline prognostic characteristics (e.g., tumor stage, PD-L1 expression level by investigational VENTANA PD-L1 (SP263) CDx assay, chemotherapy regimen before randomization, histology, smoking history, and ECOG Performance Staus) on duration of investigator-assessed DFS and OS will be examined in the PHAS and FAS. Summaries of DFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median survival time will be produced separately for each level of the cagegorical variables.

9.3.4.3 DFS and OS Rate at Other Timepoints

In addition to the DFS rate at 3-year, 5-year and 7-year as secondary endpoints, the DFS and OS rate (for example 3-, 5-, and 7-year) at various other timepoints in the PHAS and FAS may be estimated by the Kaplan-Meier methodology for each treatment arm, with two-sided 95% CIs calculated using Greenwood's formula for exploratory purposes.

9.3.4.4 Biomarker Analysis

Exploratory biomarkers analysis including, but not limited to, tumor and immune-related gene signatures and circulating tumor DNA levels and dynamics. Additionally, ctDNA levels as an early indicator of disease recurrence will also be explored in this study.

9.3.5 Other Analyses

9.3.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, race/ethnicity) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.5.3 Pharmacokinetic Analyses

The PK analysis population for atezolizumab will consistent of all participants who received any dose of atezolizumab with at least 1 post-baseline atezolizumab PK assessment available. The PK analysis population for tiragolumab will consistent of all participants who received any dose of tiragolumab with at least 1 post-baseline tiragolumab PK assessment available. Samples will be collected for PK analyses, and serum concentrations of atezolizumab and tiragolumab 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 atezolizumab and tiragolumab concentrations will be plotted for PK-evaluable participants by day.

9.3.5.4 Immunogenicity Analyses

The immunogenicity analyses will include participants with any ADA assessments, with participants grouped according to treatment received. The numbers and proportions of treatment-emergent ADA-positive participants and ADA-negative participants for both tiragolumab and atezolizumab will be summarized. The relationship between ADA status and safety, efficacy, and PK endpoints may be analyzed and reported via descriptive statistics.

9.4 INTERIM ANALYSES

The interim analyses of investigator-assessed DFS in the PHAS and FAS will be conducted by an iDCC (independent data coordinating center) and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

One interim analysis is planned for investigator-assessed DFS in the PHAS and FAS. The planned interim analysis of DFS will be conducted when approximately 249 DFS events have occurred in the PHAS (77% of the total planned DFS events) and approximately 539 DFS events have occurred in the FAS (83% of the total planned DFS events), whichever occurs later. This interim analysis is estimated to occur approximately 90 months after the first participant is enrolled in the study.

The final DFS analysis will be conducted when approximately 322 DFS events have occurred in the PHAS and approximately 652 DFS events have occurred in the FAS,

whichever occurs later. This is estimated to occur approximately 120 months after the first participant is enrolled in the study.

The stopping boundaries for the interim and final analyses of DFS are computed using the Generalized Haybittle-Peto boundaries (Haybittle 1971) with unequal two-sided p-values of 0.0260 and 0.0252 for the PHAS, and 0.0090 and 0.0071 for the FAS, in the order of analysis. If the PHAS achieves statistical significance, then α is recycled to the FAS, and the two-sided p-values for the FAS are 0.0250 and 0.0436. If the FAS achieves statistical significance, then α is recycled to the PHAS, and the two-sided p-values for the PHAS are 0.0350 and 0.0331. The corresponding statistical boundaries are shown in Table 8. The actual HR boundaries will be determined from the actual number of events observed at the time of the analyses.

The timing and statistical details for the interim analysis will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

Table 8 Analysis Timing and Stopping Boundaries for Investigator-assessed Disease-Free Survival

Type of Analysis	Time from FPI (months)	PHAS			FAS		
		Planned Events (Information fraction)	Stopping Boundary HR (2-sided p value)		Planned Events (Information fraction)	Stopping Boundary HR (2-sided p value)	
			Two sided α of 0.038	Two sided α of 0.05 [a]		Two sided α of 0.012	Two sided α of 0.05 [a]
DFS interim analysis	90	249 (77%)	HR≤0.754 (p≤0.0260)	HR≤0.766 (p≤0.0350)	539 (83%)	HR≤0.799 (p≤0.0090)	HR≤0.824 (p≤0.0250)
DFS final analysis	120	322 (100%)	HR≤0.779 (p≤0.0252)	HR≤0.789 (p≤0.0331)	652 (100%)	HR≤0.810 (p≤0.0071)	HR≤0.854 (p≤0.0436)

FPI=first participant in; PHAS=PD-L1 high analysis set; FAS=full analysis set.

[a] If α is recycled to PHAS or FAS.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 Code of Federal Regulations (CFR) (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or their legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or their legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 400 sites globally will participate to enroll approximately 1150 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. An IRF will collect, store, and potentially review imaging data.

An iDMC will be employed to monitor and evaluate participant safety throughout the study.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic case report form (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes,and lymphocytes) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, troponin I or T, creatine phosphokinase, and lactate dehydrogenase • Coagulation: INR and aPTT • Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 • C-reactive protein • HIV serology: HIV1 antibody and HIV2 antibody, or HIV1/2 antibody for all individuals • HIV RNA and CD4+ T cell count: for individuals with a positive HIV antibody test • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals • HBV DNA: for individuals with a negative HBsAb test and a positive total HBcAb test • HCV serology: HCV antibody for all individuals • HCV RNA: for individuals with a positive HCV antibody test • EBV serology: EBV VCA IgM, and EBV VCA IgG or EBNA for all individuals • EBV PCR: only if clinically indicated • Pregnancy test: all female participants of childbearing potential will have a serum pregnancy test at screening (within 14 days prior to study treatment). Urine pregnancy tests will be performed at specified subsequent visits (see Section 1.3, Table 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test • Urinalaysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)

EBV = Epstein-Barr virus; EBNA = EBV nuclear antigen; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IgM = Immunoglobulin M; INR = international normalised ratio; PCR = polymerase chain reaction; VCA = viral capsid antigen.

Investigators must document their review of each laboratory safety report.

Appendix 3
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a participant or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v 6) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 6), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5 .

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5 , to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5 .

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of new anti-cancer therapy.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more 90 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as Section 8.3.1 after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment (Section A3–8), the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A3–7.1.1 Infusion-related reactions

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and cytokine release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., infusion-related reaction or cytokine release syndrome). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated IRR eCRF or CRS eCRF, as appropriate.

If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated IRR eCRF or CRS eCRF.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event

eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of condition being studied should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF UNDERLYING CANCER

Medical occurrences or symptoms of deterioration that are anticipated as part of underlying cancer at baseline should not be recorded as adverse events. However,

deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of underlying cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of underlying non-small cell lung cancer").

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
  - Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 PATIENT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from the Patient-reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE) or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse

events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

A3–7.12 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A3–8 SPECIAL SITUATIONS

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of study drug, special situations associated with tiragolumab and/or atezolizumab and any associated adverse events will be reported until 30 days after the final dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first, and serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of new anti-cancer therapy.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3–5.

A3–9 MEDICATION ERRORS

A medication error is defined as an accidental deviation in the administration of a drug (e.g., wrong dose administered, sham procedure performed in participant assigned to active drug, drug administered in wrong location, sham procedure performed incorrectly, expired drug administered).

After initiation of study drug, special situations associated with tiragolumab and/or atezolizumab and any associated adverse events will be reported until 30 days after the final dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first, and serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of a new systemic anti-cancer therapy, whichever occurs first.

The unmasked treating physician will record information about each medication error, regardless of whether it resulted in an adverse event, on a two-page paper study treatment administration worksheet. The unmasked treating physician will provide detailed information on the first page of the worksheet and will indicate on the second page that a "medication error" has occurred. The second page of the worksheet will not indicate the type of medication error or provide any other information that could reveal the participant's treatment assignment. The first page will be archived with study records that are accessible only to unmasked personnel. The second page will be forwarded to a masked site team member, who will record the medication error on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Medication errors and any associated adverse events should be reported within 30 days after the unmasked treating physician becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the medication error should be reported to the Sponsor immediately (i.e., no more than 24 hours after the unmasked treating physician becomes aware of the event), as described in Section A3–5.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

TABLE OF CONTENTS

A4–1 RISKS ASSOCIATED WITH TIRAGOLUMAB

Infusion-related reactions and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and natural killer (NK)-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Section A4–1 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

A4–1.1 INFUSION-RELATED REACTIONS

Because tiragolumab is a therapeutic mAb and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in participants treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab/placebo and atezolizumab co-infusion will be administered over 90 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Section 6.1.2 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 8 for guidance on anaphylaxis precautions and Section A4–5.3 for guidance on management of IRRs.

A4–1.2 IMMUNE-MEDIATED HEPATITIS

The use of tiragolumab to block the immune inhibitory receptor T-cell immunoreceptor with Ig and ITIM domains (TIGIT) serves to increase a baseline T-cell and NK-cell immune response, especially in combination with another checkpoint inhibitor (CPI) (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Section A4–5.3 for guidance on the management of immune-mediated hepatitis.

A4–1.3 LYMPHOPENIA

The IgG1 backbone of tiragolumab with the intact fragment crystallizable (Fc)-effector function may lead to antibody-dependent cell cytotoxicity (ADCC) mediated reduction in lymphocyte count. Lymphopenia is a potential risk with tiragolumab. Transient decreases in lymphocyte count without clinical sequelae have been observed in participants treated with tiragolumab, with or without atezolizumab. Participants with a lymphocyte count $<$ 500 cells/mL will be excluded from this study (see Section 5.1), and CBCs will be monitored regularly during the study (see Appendix 1).

A4–1.4 IMMUNE-MEDIATED ADVERSE EVENTS

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT$-/-$), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT$-/-$ and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT$-/-$ mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutic agents intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Participants with a history of autoimmune disease will be excluded from this study (see Section 5.2).

Management guidelines for individual suspected immune-mediated adverse events are provided in Section A4–5.3.

A4–1.5 EMBRYOFETAL TOXICITY

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8$+$ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies

of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

A4–2 RISK ASSOCIATED WITH ATEZOLIZUMAB

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Section Appendix 10 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A4–3 RISK ASSOCIATED WITH COMBINATION USE OF TIRAGOLUMAB AND ATEZOLIZUMAB

Based on results from clinical data with tiragolumab plus atezolizumab, there are known and potential overlapping toxicities in participants treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune CPIs to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating participants. Participants with a history of autoimmune disease will be excluded from this study (see Section 5.2). Participants previously treated with approved or experimental CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section 5.2), participants with active infection (including, but not limited to HCV, EBV, known and/or suspected chronic

active EBV infection, or tuberculosis) and/or participants with recent severe infections will be excluded from this study (see Section 5.2).

A4–4 ADVERSE EVENTS OF SPECIAL INTEREST (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 8.3
- Suspected transmission of an infectious agent by the study drug, as defined below:

– Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Myelitis
- Facial paresis

A4–5 RISKS ASSOCIATED WITH ATEZOLIZUMAB AND/OR TIRAGOLUMAB AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH TIRAGOLUMAB AND/OR ATEZOLIZUMAB

Toxicities associated or possibly associated with atezolizumab and/or tiragolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab and/or tiragolumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Participants and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in subsequent subsections.

- In general, atezolizumab and tiragolumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider withholding atezolizumab and tiragolumab for most Grade 2 toxicities and resume when symptoms and laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Withhold atezolizumab and tiragolumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day oral prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab and tiragolumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.

- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab and tiragolumab treatment, with the exception of endocrinopathies that are controlled by hormone replacement therapy.
- The investigator should consider the benefit–risk balance for a given participant prior to further administration of atezolizumab and tiragolumab. Resumption of atezolizumab and tiragolumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with atezolizumab and tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

A4–5.1 DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab and tiragolumab in this study.

A4–5.2 TREATMENT INTERRUPTION

Atezolizumab and tiragolumab treatment may be temporarily suspended in participants experiencing toxicity as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguished from one another in the clinical setting, immune-mediated adverse events should generally be attributed to atezolizumab and tiragolumab, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to atezolizumab and tiragolumab. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab and tiragolumab can be resumed. If atezolizumab and tiragolumab is withheld for $>$12 weeks after event onset, the participant will be discontinued from atezolizumab and tiragolumab. However, atezolizumab and tiragolumab may be withheld for $>$12 weeks to allow for participants to taper off corticosteroids prior to resuming treatment. Atezolizumab and tiragolumab can be resumed after being withheld for $>$12 weeks if the participant is likely to derive clinical benefit. The decision to re-challenge participants with atezolizumab and tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator. Continued dosing with single-agent atezolizumab is allowed and will require that all other study eligibility criteria continue to be met. Continue dosing with single-agent tiragolumab is not allowed. The Medical Monitor is available to advise as needed. Atezolizumab and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements

for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A4–5.3 MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Participants will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, COPD, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A4-1.

Table A4-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue tiragolumab/placebo and atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider participant referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding tiragolumab/placebo and atezolizumab. – Consider resuming on radiographic evidence of improvement.
Pulmonary event, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

Table A4-2 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
Pulmonary event, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c, d] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, tiragolumab/placebo and atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Participants eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A4-3.

Participants with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and the results reviewed before administration of the next dose of study drug(s).

For participants with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table A4-3 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Consider participant referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A4-4.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A4-4 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, initiate empiric IV corticosteroids while waiting for definitive diagnosis. • Participant referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]

Table A4-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 3	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A4-5.

Participants with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the

presence of thyroid, pituitary, or adrenal endocrinopathies. Participants should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A4-5 Management Guidelines for Endocrine Events

Event	Management
Hypothyroidism, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Hypothyroidism, Grade 2	• Consider withholding tiragolumab/placebo and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider participant referral to endocrinologist. • Resume tiragolumab/placebo and atezolizumab when symptoms are controlled and thyroid function is improving.
Hypothyroidism, Grade 3 or 4	• Withhold tiragolumab/placebo and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer participant to endocrinologist. • Admit participant to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume tiragolumab/placebo and atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]
Hyperthyroidism, Grade 1	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue tiragolumab/placebo and atezolizumab. • Monitor TSH every 4 weeks. • Consider participant referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider participant referral to endocrinologist.

Table A4-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperthyroidism, Grade 2	• Consider withholding tiragolumab/placebo and atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider participant referral to endocrinologist. • Resume tiragolumab/placebo and atezolizumab when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 or 4	• Withhold tiragolumab/placebo and atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Refer participant to endocrinologist. • Resume tiragolumab/placebo and atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and participant is stable on replacement therapy, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better or participant is not stable on replacement therapy while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue tiragolumab/placebo and atezolizumab. • Investigate for diabetes. If participant has Type 1 diabetes, treat as a Grade 3 event. If participant does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.

Table A4-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 3 or 4	• Withhold tiragolumab/placebo and atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume tiragolumab/placebo and atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (panhypopituitarism), Grade 2 or 3	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (panhypopituitarism), Grade 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A4-6.

Table A4-6 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table A4-7.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., troponin, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on immune-mediated pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All participants with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, a TTE for evaluation of left ventricular injection fraction and global longitudinal strain, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A4-7.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any participant presenting with chest pain and may be associated with immune-mediated myocarditis (see section on immune-mediated myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any participant presenting with chest pain associated with dyspnea or hemodynamic instability.

Participants should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (e.g., metastatic disease), cancer treatment (e.g., chest radiotherapy), cardiac injury (e.g., injury due to myocardial infarction or iatrogenesis), and autoimmune disorders, and should be managed accordingly.

All participants with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, TTE, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Participants with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A4-7. Withhold treatment with tiragolumab/placebo and atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A4-7 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 or Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. • Refer participant to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 g/day IV methylprednisolone for 3–5 days and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of the Day 1, Cycle 1 infusion of tiragolumab/placebo and atezolizumab. However, participants who experience an infusion-related reaction (IRR) with the Day 1, Cycle 1 infusion of tiragolumab/placebo and atezolizumab may receive premedication with antihistamines, anti-pyretic medication, or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with tiragolumab/placebo and atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within

24 hours of tiragolumab/placebo or atezolizumab administration and are generally mild to moderate in severity.

Guidelines for medical management of IRRs are provided in Table A4-8.

Table A4-8 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics and monitor closely for IRRs. [a]
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue tiragolumab/placebo and atezolizumab co-infusion and contact the Medical Monitor. [a, b]

IRR = infusion-related reaction.

[a] Tiragolumab/placebo and atezolizumab sequential infusion may be considered during subsequent infusions. In the sequential infusion, atezolizumab should be infused before tiragolumab/placebo. Instructions in Table 6 should also be followed for sequential infusion of tiragolumab/placebo and atezolizumab. Co-infusion of tiragolumab/placebo and atezolizumab may be resumed if the sequential infusion is tolerated.

[b] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of tiragolumab/placebo and atezolizumab. However, participants who experience cytokine-release syndrome (CRS) with tiragolumab/placebo and atezolizumab may receive premedication with antihistamines, anti-pyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

Guidelines for medical management of CRS are provided in Table A4-9.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). If a participant develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table A4-9 Management Guidelines for Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in participants with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for CRS.
Grade 2 [a] Fever [b] with at least one of the following: • Hypotension not requiring vasopressors • Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize participant (monitoring in the ICU is recommended), permanently discontinue tiragolumab/placebo and atezolizumab, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of tiragolumab/placebo and atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Table A4-8 Management Guidelines for Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with at least one of the following: • Hypotension requiring a vasopressor (with or without vasopressin) • Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS . • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize participant until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for participants who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with at least one of the following: • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For participants who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize participant until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on the ASTCT CRS consensus grading scale. NCI CTCAE v5.0 and the ASTCT CRS consensus grading scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine-Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In participants who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretic medications, and/or analgesics, and monitor closely for CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A4-10.

Table A4-10 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue tiragolumab/placebo and atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]

Table A4-11 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to gastrointestinal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab and/or tiragolumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A4-12.

Table A4-12 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue tiragolumab/placebo and atezolizumab. • Consider participant referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold tiragolumab/placebo and atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring participant to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue tiragolumab/placebo and atezolizumab.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Myasthenia may be associated with myositis (see section on immune-mediated myositis), and patients should be managed accordingly. Management guidelines for neurologic disorders are provided Table A4-13 with specific guidelines for myelitis provided in Table A4-15.

Table A4-13 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Table A4-14 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer participant to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • For facial paresis: – Initial observation OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain. – If event resolves fully, resume tiragolumab/placebo and atezolizumab [b] If event does not resolve fully while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to neurologist. • Initiate treatment as per institutional guidelines and proceed as per Guillain-Barré syndrome management.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone. • Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms. • In life-threatening cases, consider IV methylprednisone 1 g/day for 3–5 days and consider other immunosuppressive agent.

IVIG = intravenous immunoglobulin.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A4-15 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue tiragolumab/placebo and atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. • Initiate non-opiod treatment (e.g., pregabalin, gabapentin, duloxetine) for pain. • Hospitalize participant – Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone. – If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage treatment as per institutional guidelines. • Refer participant to neurologist

IVIG = intravenous immunoglobulin.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A4-16.

Table A4-16 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. • Refer participant to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

RENAL EVENTS

Eligible participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A4-17.

Table A4-17 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Monitor kidney function closely, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset. [a] • Refer participant to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/creatine phosphokinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Participants may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis. Participants with possible myositis should be referred to a rheumatologist or neurologist. Participants with possible myositis should be monitored for signs of myocarditis (see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A4-18.

Table A4-18 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue tiragolumab/placebo and atezolizumab. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Table A4-19 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 2	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold tiragolumab/placebo and atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Consider IVIG or plasmapheresis. • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tiragolumab/placebo and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab/placebo and atezolizumab, permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c]

Table A4-20 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. [c] • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • Consider IVIG or plasmapheresis. • If event does not improve within 24−48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IVIG = intravenous immunoglobulin.

[a] Tiragolumab/placebo and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before tiragolumab/placebo and atezolizumab can be resumed.

[c] Resumption of tiragolumab/placebo and atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tiragolumab/placebo and atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH)

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant should be classified as having HLH if five of the following eight criteria are met:

Fever ≥38.5°C

Splenomegaly

Peripheral blood cytopenia consisting of at least two of the following:

- Hemoglobin <90 g/L (9 g/dL)
- Platelet count $<100\times10^9$/L ($<100{,}000/\mu$L)
- ANC $<1.0\times10^9$/L ($<1000/\mu$L)

Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)

Hemophagocytosis in bone marrow, spleen, lymph node, or liver

Low or absent natural killer cell activity

Ferritin >500 mg/L (500 ng/mL)

Soluble IL-2 receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Participants with suspected HLH should be treated according to the guidelines in Table A4-21.

Table A4-21 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• Permanently discontinue tiragolumab/placebo and atezolizumab and contact the Medical Monitor. • Consider participant referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis;

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study, within 90 days after the final dose of tiragolumab, and within 5 months after the final dose of atezolizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within after the final dose of 90 days after the final dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Sharing of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy

Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment (or the female partner of a male participant exposed to study treatment) should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment (or the female partner of a male participant exposed to study treatment) should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Clinical Outcome Assessment Instrument(s)

TABLE OF CONTENTS

A6–1 CLINICAL OUTCOME ASSESMENT INSTRUMENT(S)

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the appropriate instruments to be administered in the correct order at each specified timepoint.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 20-25 minutes at each specified visit during the first year of treatment, and 15-20 minutes at each specified visit in the following years.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

Site staff should review all completed instruments and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants to complete the item or confirm that the item was intentionally left blank.

Additionally, data collection via an alternate method (e.g. telephone) may be used during safety follow-up or long-term follow-up visits and in exceptional circumstances (e.g. if the participant cannot visit the site). Source documentation should be obtained, which includes, among other information, that the questionnaires were administered by the alternate method (e.g. telephone).

A6–1.1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

A6–1.2 EORTC QLQ-LC13

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

A6–1.3 EORTC IL46

ENGLISH

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

A6–1.4 PRO-CTCAE (SELECTED ITEMS)

NCI-PRO-CTCAE® CUSTOM SURVEY

Item subset derived from PRO-CTCAE® Item Library Version 1.0
English
Form Created on 21-June-2023
https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

6a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, did you have any RASH?	
O Yes	O No

9a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

11a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
11b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, how OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12c. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				

O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

13a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
13b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
14b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

15a. In the last 7 days, how OFTEN did you feel ANXIETY?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
15b. In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
15c. In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

16a. In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
16b. In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
16c. In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

17a. In the last 7 days, did you HAVE ANY PAIN, SWELLING, OR REDNESS AT A SITE OF DRUG INJECTION OR IV?		
O Yes	O No	O Not applicable

A6–1.5 EUROQOL EQ-5D-5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

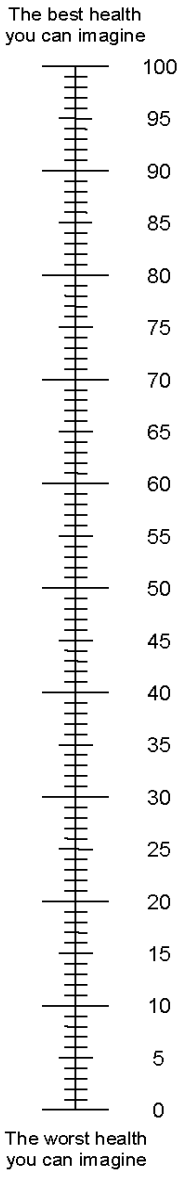
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7 AJCC/UICC Non-Small Cell Lung Cancer Staging, 8th Edition

American Joint Committee on Cancer(AJCC)/Union Internationale Contre le Cancer (UICC) non–small cell lung cancer (NSCLC) Staging, 8th edition.

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis**[e]
M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition are in bold.
[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.

Appendix 7: AAJCC/UICC Non Small Cell Lung Cancer Staging, 8th Editionlinical Outcome Assessment Instrument(s)

		N categories			
		Overall stage			
Descriptor in 7th edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a]Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

Appendix 8
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

1. In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:
2. Stop the study treatment administration, if possible.
3. Call for additional medical assistance.
4. Maintain an adequate airway.
5. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
6. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
7. Continue to observe the participant and document observations.
8. Collect serum samples for immunogenicity testing.
9. Ask the participant to return for immunogenicity sample collection at the time of washout, if appropriate.

Appendix 9
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to atezolizumab and tiragolumab or NSCLC and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to atezolizumab and tiragolumab, treatments of this drug class, or further our understanding of NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

DNA samples will be analyzed for somatic (non-inherited) mutations that are specific to the tumor that will allow circulating tumor (ctDNA) to be tracked in the blood. The presence and change in ctDNA levels will be analyzed for any association with response to study treatment, DFS and overall survival (OS). ctDNA levels or dynamics will also be analyzed for any association with disease recurrence. Newly acquired somatic mutations will also be identified to understand potential mechanisms of resistance to treatment. Overall, these analyses will help to develop better early tests for NSCLC, to identify participants that will benefit most from this specific treatment and to improve future therapies of this class for NSCLC. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to atezolizumab and tiragolumab or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on atezolizumab and tiragolumab or treatments of this drug class or NSCLC continues but no longer than 10 years or other period as per local requirements.

Appendix 10
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A10-1 Investigational Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Tiragolumab placebo	IMP (placebo)	Unauthorized	Not applicable

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab monotherapy is approved as adjuvant treatment for participants with PD-L1 high (≥ 50% TC) NSCLC.

Table A10-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Tiragolumab placebo	IMP (placebo)	Unauthorized	Not applicable

AxMP = auxiliary medicinal product; IMP = investigational medicinal product; UK = United Kingdom.

[a] Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab monotherapy is approved as adjuvant treatment for participants with PD-L1 high (≥ 50% TC) NSCLC.

Appendix 11 Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Granulomatosis with polyangiitis • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 12 Recommendations for Adjuvant Chemotherapy

Other dosing regimens can be considered if consistent with approved drug labels specific for adjuvant treatment of NSCLC.

Preferred (nonsquamous)

- Cisplatin 75 mg/m^2 Day 1, Pemetrexed 500 mg/m^2 Day 1 every 21 days for 4 cycles

Preferred (squamous)

- Cisplatin 75 mg/m^2 Day 1, Gemcitabine 1250 mg/m^2 Days 1 and 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m^2 day 1, Docetaxel 75 mg/m^2 day 1 every 21 days for 4 cycles

Other Recommended

- Cisplatin 50 mg/m^2 days 1 and 8, Vinorelbine 25 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles
- Cisplatin 100 mg/m^2 day 1, Vinorelbine 30 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles
- Cisplatin 75–80 mg/m^2 day 1, Vinorelbine 25–30 mg/m^2 days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m^2 day 1, Etoposide 100 mg/m^2 days 1–3, every 28 days for 4 cycles

Useful in Certain Circumstances

Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy

- Carboplatin AUC 6 day 1, Paclitaxel 200 mg/m^2 day 1, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, Gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, Pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles (nonsquamous histology)

Appendix 13
Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
BEN	benign ethnic neutropenia
BICR	blinded independent central review
BSC	best supportive care
CDx	Companion Diagnostics
CFR	Code of Federal Regulations
CIT	cancer immunotherapy
CLIA	Clinical Laboratory Improvement Amendments
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus 2019
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DFS	disease-free survival
DLT	Dose-limited toxicity
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report Form
EDC	electronic data capture
EFS	Event free survival
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GHS	global health status
HBcAb	hepatitis B core antibody

Appendix 13: Abbreviation

Abbreviation or Term	Definition
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
iDMC	Independent data monitoring committee
IFN	interferon
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LACE	Lung Adjuvant Cisplatin Evaluation
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MLND	mediastinal lymph node dissection
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generational sequencing
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PBS	Pharma Biosample Services
pCR	pathological complete response
PCR	polymerase chain reaction
PET	positron emission tomography

Appendix 13: Abbreviation

Abbreviation or Term	Definition
PFS	progression-free survival
PHAS	PD-L1 high analysis set
PK	pharmacokinetic
PORT	postoperative radiotherapy
PR	partial response
PRO	participant-reported outcome
PVR	poliovirus receptor
Q3W	every 3 weeks
Q4E	Every 4 weeks
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small cell lung cancer
SOC	standard of care
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TNF-α	tumor necrosis factor–α
TPS	tumor proportion score
ULN	upper limit of normal
VAS	visual analog scale
WES	whole exome sequencing
WGS	whole genome sequencing

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