

**Official 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

**NCT Number:** NCT06267001

**Document Date:** Protocol Amendment Version 2: 06-Sep-2024

## 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:** 2

**TEST PRODUCTS:** Tiragolumab (RO7092284)  
Atezolizumab (RO5541267)

**STUDY PHASE:** Phase III

**REGULATORY AGENCY IDENTIFIERS:** IND Number: 129258  
EU CT Number: 2023-506696-10-00  
PS ID: PS-24-01-045854  
NCT Number: NCT06267001

**SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:** F. Hoffmann-La Roche Ltd  
Grenzacherstrasse 124  
4058 Basel, Switzerland

**APPROVAL:** See electronic signature and date stamp on the final page of this document.

## CONFIDENTIAL

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## PROTOCOL HISTORY

| Protocol |   |
|----------|---|
| Version  | Date Final  |
| 2        | See electronic date stamp on final page of this document. |
| 1        | 18 August 2023  |

## **PROTOCOL AMENDMENT, VERSION 2: RATIONALE**

In July 2024, the Sponsor made the decision not to continue the GO45006 study as originally planned and to initiate the phase out process. As a result, enrollment was closed on 6 September 2024. Patients will be allowed to continue to receive study treatment, at the discretion of the investigator, and will then remain on study until they have completed the safety follow-up period. Protocol GO45006 has been amended primarily to reflect associated changes in the study design, objectives and estimands/endpoints, study assessments and planned analyses because of the decision to phase out the study. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- Because of the decision to phase out Study GO45006, the following changes have been introduced:
  - The primary objective of the study has been updated to a sole primary objective of safety to reflect the change in scope because of the decision to phase out the study. [REDACTED]
  - The estimated number of patients to be enrolled has been updated to approximately up to [REDACTED] participants, [REDACTED] (Sections 1.2 [Figure 1], 4.1, and 5).
  - The schedule of activities (SoA) has been updated to add pregnancy testing at the treatment discontinuation/completion visit and magnesium to the chemistry laboratory panel, as they were previously omitted. [REDACTED] (Section 1.3 [Table 1]).
  - The schedule for disease assessments has been updated to be performed as per local standard practice to reduce the burden to sites and patients because disease free survival (DFS) will no longer be analyzed (Section 1.3 [Table 1], 4.1, and 8.1.1).
  - Text has been updated to indicate Study GO45006 is being phased out and participants on study or about to enroll at the time of the decision will be allowed to continue receiving study treatment or to proceed with screening and enrollment (Sections 2.1 and 3).

- The independent data monitoring committee (iDMC) will no longer be needed and the associated language has been removed. Language has been added to clarify how safety will be monitored for the remaining patients (Sections 2.3, 4.1, 6.3.2, 9.4, A1-5).
- Language has been added to clarify that the study will be unblinded and what the treatment options are for patients who remain on study. Information on unblinding for medical emergencies and non-emergencies has also been removed as it is no longer applicable (Sections 4.1, 6.1, and 6.3.2).
- Language related to the use of an independent review facility (IRF) and blinded independent central review (BICR) has been removed as it is no longer applicable (Sections 1.3 [Table 1], 4.1, 8.1.1, and A1-5).
- The end of study definition and duration of participation has been updated to reflect the decision not to continue as originally planned and to phase out the study Sections 4.4 and 4.5).
- Text has been deleted regarding partial withdrawal because it is no longer applicable for patients on study treatment (Section 7.2).
- Text has been added to clarify remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report. For individuals who are not enrolled (screen failed), remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination (Section 8.7).
- The statistical considerations section has been updated to reflect that no statistical hypothesis testing will be performed for the study.


[REDACTED]

- Text has been updated to provide guidance in the collection and reporting of adverse events and serious adverse events related to the investigational in vitro device (IVD) [REDACTED] (Sections 8.3.1 and 8.3.2, and Appendices A3-5.1, A3-5.2, and A3-6).
- Missing rationale for the collection of race and ethnicity data has been provided in new Section 4.2.4.
- Text has been updated to clarify that individuals with a valid, negative PD-L1 result by central testing cannot be re-screened unless there are clear technical reasons for why re-screening is needed (Section 5.4).
- Text has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 6.6).

- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.3.4).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 21 (Appendix 4).
- An appendix with administrative information about laboratories involved in testing, analysis, and biosample destruction in China has been added to satisfy Human Genetic Resources Administration of China (HGRAC) requirements (Appendix 12).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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## PROTOCOL AMENDMENT 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

**PROTOCOL NUMBER:** GO45006

**STUDY NAME:** SKYSCRAPER-15

**VERSION NUMBER:** 2

**TEST PRODUCT(S):** Tiragolumab (RO7092284)  
Atezolizumab (RO5541267)

**SPONSOR NAME:** F. Hoffmann-La Roche Ltd

**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: PS-24-01-045854  
NCT Number: NCT0626700

### STUDY RATIONALE

The *original* purpose of this study *was* to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered to participants with PD-L1 positive ( $\geq 1\%$  tumor cells [TC] [REDACTED] Stage IIB, IIIA and select IIIB (T3N2) non–small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy.

*As communicated to sites and investigators in July 2024, the Sponsor has decided not to continue study GO45006 as originally planned and to initiate the phase out process. Participants on study or considered for enrollment at the time of the decision will be allowed to continue receiving study treatment or proceed with screening and enrollment. The GO45006 protocol has been amended throughout to reflect this change.*

### OBJECTIVES AND ENDPOINTS

| <i>Primary Objective</i>  | <i>Corresponding Endpoint</i>  |
|---|--|
| <ul style="list-style-type: none"><li>To evaluate the safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab</li></ul> | <ul style="list-style-type: none"><li>Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0</li></ul> |

### OVERALL DESIGN AND STUDY POPULATION

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

*Following the Sponsor's decision to phase out the study, the objective of the study is to ensure the treatment continuity and safety for the participants who continue to receive study treatment.*

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

|                              |                             |   |  |
|------------------------------|-----------------------------|---|--|
| <b>Phase:</b>                | Phase III                   | <b>Population Type:</b>                       | Adult population   |
| <b>Control Method:</b>       | Placebo                     | <b>Population Diagnosis or Condition:</b>     | Participants with PD-L1 $\geq$ 1% TC Stage IIB, IIIA, or select IIIB (T3N2 only) NSCLC following resection and adjuvant platinum-based chemotherapy. |
| <b>Interventional Model:</b> | Parallel group              | <b>Population Age:</b>                        | $\geq$ 18 years  |
| <b>Test Products:</b>        | Tiragolumab<br>Atezolizumab | <b>Site Distribution:</b>                     | Multi-site   |
| <b>Active Comparator:</b>    | Placebo<br>Atezolizumab     | <b>Study Intervention Assignment Method:</b>  | Randomization  |
| <b>Number of Arms:</b>       | 2                           | <b>Number of Participants to Be Enrolled:</b> | Approximately 60   |

### **STUDY TREATMENT**

Tiragolumab or placebo will be administered as 600 mg/10 mL, 840 mg every four weeks (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 Q4W

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

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

### **DURATION OF PARTICIPATION**

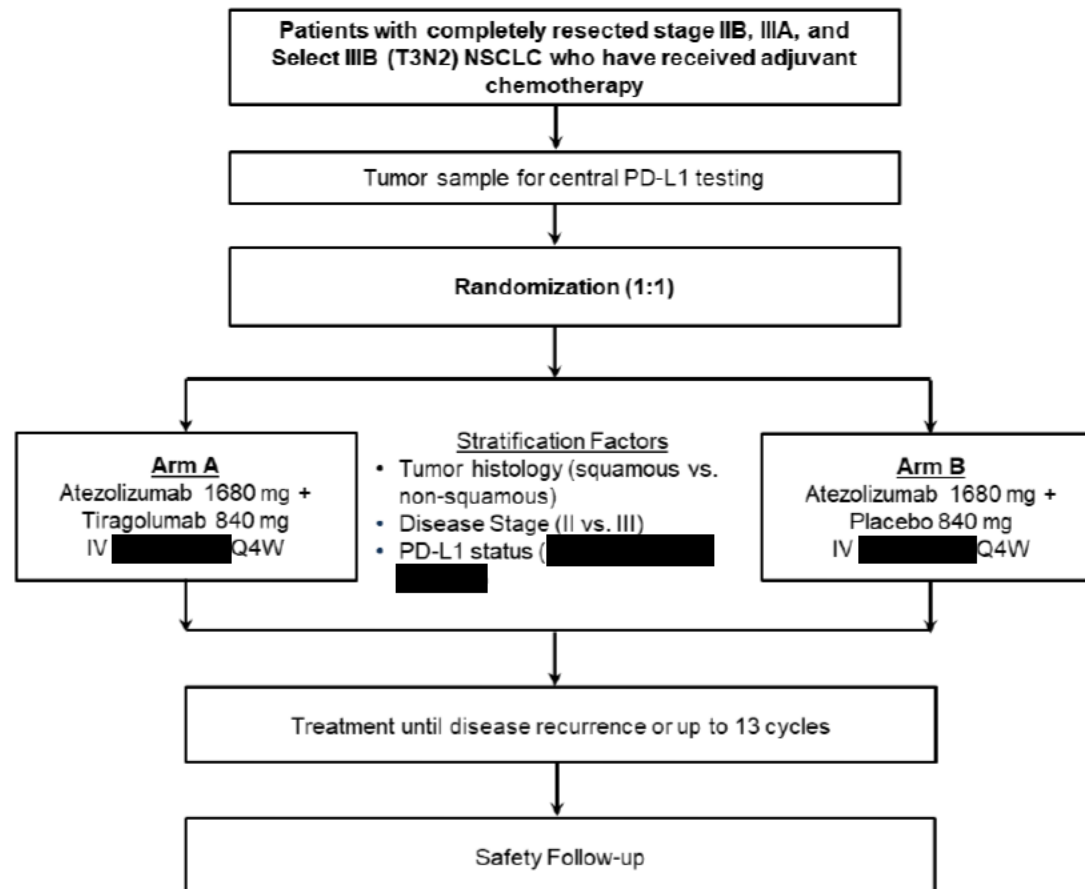
*Participation will continue until completion of safety follow-up, withdrawal or death due to any cause, whichever occurs first.*

### **COMMITTEES**

|                                |                |
|--------------------------------|----------------|
| <b>Independent Committees:</b> | Not applicable |
| <b>Other Committees:</b>       | 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 <sup>a</sup> |                  | Treatment (28-Day Cycles) <sup>b</sup>            | Treatment Discontinuation/<br>Completion <sup>c</sup> | <i>Safety</i> Follow-Up |
|---|--------------------|------------------------|------------------|---|---|-------------------------|
|   |                    | Days – 28 to – 1       | Days – 14 to – 1 | Day 1 (every 28 days)<br>(± 3 days for Cycle ≥ 2) | ≤ 30 Days After Final Dose                            |                         |
| Signed ICF(s) <sup>d</sup><br>- main ICF signing may occur up to 60 days prior to randomization | Section 8 and A1–3 | x                      |                  |   |   |                         |
|   | Section 8.7        | x                      |                  |   |   |                         |
| <i>EGFR</i> and <i>ALK</i> mutational status (if applicable)                                    | Section 4.1        | x                      |                  |   |   |                         |
| Demographics  | Section 8          | x                      |                  |   |   |                         |
| Medical history   | Section 8          | x                      |                  |   |   |                         |
|   | Appendix 2         | x                      |                  |   |   |                         |
|   | Appendix 2         | If applicable          |                  |   |   |                         |
| CD4 + T-cell count  | Appendix 2         | If applicable          |                  |   |   |                         |
|   | Appendix 2         | If applicable          |                  | If applicable                                     | If applicable   |                         |
|   | Appendix 2         | If applicable          |                  |   |   |                         |

**Table 1 Schedule of Activities (cont.)**

| Assessment/Procedure   | Protocol Reference           | Screening <sup>a</sup> |                     | Treatment (28-Day Cycles) <sup>b</sup>                            | Treatment Discontinuation/ Completion <sup>c</sup>                       | Safety 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   |                  |
| Urinalysis (dipstick permitted) (specific gravity, pH, glucose, protein, ketones, and blood) | Appendix 2                   | x                      |                     | As clinically indicated   |  |                  |
| Pregnancy test (women of childbearing potential only) <sup>g, h</sup>                        | Section 8.2.5 and Appendix 2 |                        | Serum test required | Serum or urine test (if positive, serum test required to confirm) | <i>Serum or urine test (if positive, serum test required to confirm)</i> |                  |
| ECG  | Section 8.2.3                | x                      |                     | As clinically indicated   |  |                  |
| Concomitant medications  | Section 6.8                  | x                      |                     | x   | x  |                  |
| ECOG Performance Status <sup>h</sup>   | 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                      |                     |   |  |                  |
| Limited physical examination, weight <sup>h</sup>  | Section 8                    |                        |                     | x   | x  |                  |

**Table 1 Schedule of Activities (cont.)**

| Assessment/Procedure   | Protocol Reference           | Screening <sup>a</sup> |                  | Treatment (28-Day Cycles) <sup>b</sup>   | Treatment Discontinuation/ Completion <sup>c</sup> | Safety 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                         |                  |
| Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) <sup>g, h</sup>   | 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, <i>magnesium</i> , glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH) <sup>g, h</sup> | Section 8.2.4 and Appendix 2 |                        | x                | x  | x  |                  |
|  | Appendix 2                   | x                      |                  | x  | x  |                  |
|  | Appendix 2                   | x                      |                  | x  | x  |                  |
| TSH, free T3 (or total T3), and free T4 <sup>h</sup>   | 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  |                  |

**Table 1 Schedule of Activities (cont.)**

| Assessment/Procedure                         | Protocol Reference           | Screening <sup>a</sup>  |                  | Treatment (28-Day Cycles) <sup>b</sup>         | Treatment Discontinuation/Completion <sup>c</sup> | Safety 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                        |                  |
| Coagulation tests: INR and aPTT <sup>g</sup> | 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 <sup>i</sup>              | Section 8.1.1                | Disease assessments will be performed at screening and at a frequency per local standard practice during the study treatment period. Disease assessments should continue per local standard practice until disease recurrence, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. |                  |  |   |                  |
| Adverse events                               | Section 8.3 and Appendix 3   |   | x                | x  | x   | x <sup>k</sup>   |

ALK=anaplastic lymphoma kinase; C=cycle; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; D=day; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; FFPE=formalin fixed paraffin embedded;

ICF=informed consent form; LC=lung cancer; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1.

**Table 1 Schedule of Activities (cont.)**

- <sup>a</sup> 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.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> 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.
- <sup>e</sup> [REDACTED]
- <sup>f</sup> [REDACTED]
- <sup>g</sup> Specified screening laboratory test results must be obtained within 14 days of randomization.
- <sup>h</sup> 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. [REDACTED]
- <sup>i</sup> [REDACTED]
- <sup>j</sup> In rare cases where iodine contrast is contraindicated: CT chest non-contrast plus MRI abdomen preferred; CT chest/abdomen non-contrast acceptable.

## Table 1 Schedule of Activities (cont.)

<sup>k</sup> 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. After initiation of study treatment, all adverse events will be reported until ■ days after the final dose of study treatment ■, and serious adverse events will continue to be reported until ■ days after the final dose of study treatment ■. In addition, adverse events of special interest will continue to be reported until ■ days after the final dose of study treatment, ■. After this period, all deaths, regardless of cause, should be reported. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the adverse event should be reported. 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 patient is lost to follow up, or the patient 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.

## **2. INTRODUCTION**

### **2.1 STUDY RATIONALE**

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

*As communicated to sites and investigators in July 2024, the Sponsor has decided not to continue study GO45006 as originally planned and to initiate the phase out process. Participants on study or considered for enrollment at the time of the decision will be allowed to continue receiving study treatment or proceed with screening and enrollment. The GO45006 protocol has been amended throughout to reflect this change.*

#### **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 6](#)). The Lung Adjuvant Cisplatin Evaluation 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  $\geq 4$  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 selected 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 survival 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 currently 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  $\geq 1\%$  of tumor cells (TC) (in the US, Japan and other countries) or PD-L1 expression on  $\geq 50\%$  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  $\geq 1\%$  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  $\geq 50\%$  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  $\geq 1\%$  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  $\geq 50\%$  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  $\geq 4$  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  $\geq 50\%$  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  $\geq 50\%$  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 adjuvant 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.

Tiragolumab was further evaluated in participants with PD-L1 selected advanced NSCLC ( $\geq 1\%$  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 ( $\geq 10\%$  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/ $\kappa$  monoclonal antibody (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 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 *was originally* 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 ( $\geq 1\%$  TC by [REDACTED]) 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  $\geq 1\%$  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, [REDACTED]

[REDACTED] Tiragolumab plus atezolizumab 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. [REDACTED]

[REDACTED] 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. [REDACTED]

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 tiragolumab 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 [8.3.9](#)).

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 *was designed to* 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)- $\gamma$  (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 *checkpoint inhibitor*), 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 *was originally designed to* 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 ( $\geq 1\%$  TC by [REDACTED])

[REDACTED] who have received adjuvant platinum-based chemotherapy.

*In light of the upcoming study phase-out, the Sponsor has decided to streamline the GO45006 study protocol. Accordingly, the primary objective of the study has been updated to a single safety objective (Table 2).*

**Table 2 Primary Objective and Corresponding Endpoint**

| <i>Primary Objective</i>  | <i>Corresponding Endpoint</i>  |
|---|--|
| <ul style="list-style-type: none"><li>To evaluate the safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab</li></ul> | <ul style="list-style-type: none"><li>Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0</li></ul> |

NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

### 4. **STUDY DESIGN**

#### 4.1 **OVERALL DESIGN**

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

*Following the Sponsor's decision to phase out the study, the objective of the study is to ensure the treatment continuity and safety for the participants who continue to receive study treatment (Section 3).*

The study schema is shown in [Figure 1](#) (Section 1.2). The schedule of activities is provided in [Table 1](#) (Section 1.3).

Male and female participants age  $\geq 18$  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  $\geq 1\%$  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 [REDACTED]. Only participants with PD-L1 expression  $\geq 1\%$  TC by [REDACTED] 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.

*Following the Sponsor's decision to phase out the study, patients in pre-screening or screening can be randomized and enrolled if they are eligible per the study inclusion criteria. An estimated [REDACTED] patients will be enrolled.*

[REDACTED] Eligible participants will be randomized in a 1:1 ratio to either the experimental arm (tiragolumab plus atezolizumab) or the comparator arm (placebo plus atezolizumab). Participants should receive their first dose of study treatment on the day of randomization if possible. [REDACTED]

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 ([REDACTED]).

*As a result of the decision to phase out the study, the study will be unblinded. After participants have been unblinded and at the discretion of the investigator, participants randomized to the comparator arm may discontinue placebo and continue with atezolizumab monotherapy (1680 mg by IV infusion on Day 1 of each 28-day cycle) for a total of 13 cycles, approximately 1 year, in the absence of disease recurrence, or unacceptable toxicity. Participants randomized to the experimental arm, may at the discretion of the investigator, discontinue tiragolumab or continue to receive tiragolumab and atezolizumab (840 mg and 1680 mg respectively) by IV [REDACTED] on*

*Day 1 of each 28-day cycle for a total of 13 cycles, approximately 1 year, in the absence of disease recurrence, or unacceptable toxicity.*

Crossover from the *comparator* arm to the *experimental* arm will not be allowed.

All participants will undergo scheduled disease assessment scans by computed tomography (CT) at screening *and per local standard practice during the study treatment period*. Disease assessments will continue *per local standard practice* until disease recurrence, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

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.

After initiation of study treatment, all adverse events will be reported until [REDACTED] days after the final dose of study treatment [REDACTED]. Serious adverse events will continue to be reported until [REDACTED] days after the final dose of study treatment [REDACTED]. In addition, adverse events of special interest will continue to be reported until [REDACTED] days after the final dose of study treatment, [REDACTED]. 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.

*The Sponsor will monitor patient safety throughout the study. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events; deaths; vital signs; and laboratory abnormalities, the Sponsor will review all cumulative data at regular intervals during the study.*

## **4.2 RATIONALE FOR STUDY DESIGN**

This is a Phase III, randomized, double-blind, global, multicenter study *originally* designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab compared with placebo plus atezolizumab administered to participants with PD-L1  $\geq 1\%$  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  $\geq 1\%$  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 $\geq 1\%$ TC Status**

In the IMpower010 study, adjuvant atezolizumab demonstrated a statistically significant DFS benefit over BSC in participants with Stage II–IIIA NSCLC whose tumors expressed PD-L1 on  $\geq 1\%$  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 BSC 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**

*With the decision to phase out the GO454006 study, the primary endpoint of the study has been updated to safety (Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0).*

#### **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 [REDACTED] by central testing. Published results suggest that the expression of PD-L1 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).

#### **4.2.4            Rationale for Collection of Information on Race and Ethnicity**

*Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of these data may contribute to a better understanding of the distribution of NSCLC according to race or ethnicity.*

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



- Participants must have had complete resection of NSCLC (no residual tumor and all surgical margins negative for invasive carcinoma)
  - [REDACTED]
  - [REDACTED]
- 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. [REDACTED]
  - [REDACTED]
  - [REDACTED]
- 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 11](#)).
- Participants must have recovered adequately from surgery and from adjuvant chemotherapy (no Grade >2 unresolved toxicity)
  - [REDACTED]
- [REDACTED]
- [REDACTED]
- Tumor PD-L1 expression with a  $\geq 1\%$  TC as determined by [REDACTED], documented through central testing of a representative tumor tissue specimen
  - [REDACTED]

- [REDACTED]
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - [REDACTED]
    - [REDACTED]
  - [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
  - [REDACTED]
    - [REDACTED]
    - [REDACTED]
  - [REDACTED]
    - [REDACTED]

- [REDACTED]
- 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 ICF.

- 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 ICF.

## 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:

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

- 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, [REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- 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
- [REDACTED]
- 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 [REDACTED] to initiation of study treatment
- Prior treatment with [REDACTED]  
[REDACTED]
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within [REDACTED] (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- $\alpha$  [TNF- $\alpha$ ] agents) [REDACTED] prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [REDACTED]  
[REDACTED]
  - [REDACTED]  
[REDACTED]
- 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/placobo or within 5 months after the final dose of atezolizumab
- [REDACTED]  
[REDACTED]
- 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](#)).

*Individuals with a valid, negative PD-L1 result by central testing cannot be re-screened unless there are clear technical reasons for why re-screening is needed.*

## **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 9](#)).

### **6.1 STUDY TREATMENT ADMINISTERED**

[Table 3](#) provides a description of assigned study treatments for this study. *After participants have been unblinded and at the discretion of the investigator, participants randomized to the comparator arm may discontinue placebo and continue with atezolizumab monotherapy. Participants randomized to the experimental arm, may at the discretion of the investigator, discontinue tiragolumab or continue to receive tiragolumab and atezolizumab.*

**Table 3 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                 | ■ mL glass vials         | ■ mL glass vials    | ■ mL glass vial or ■ 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 *treatment or* combination of treatments participants *receive* as part of this study (i.e., atezolizumab plus tiragolumab, *atezolizumab plus placebo*, or *atezolizumab monotherapy*).

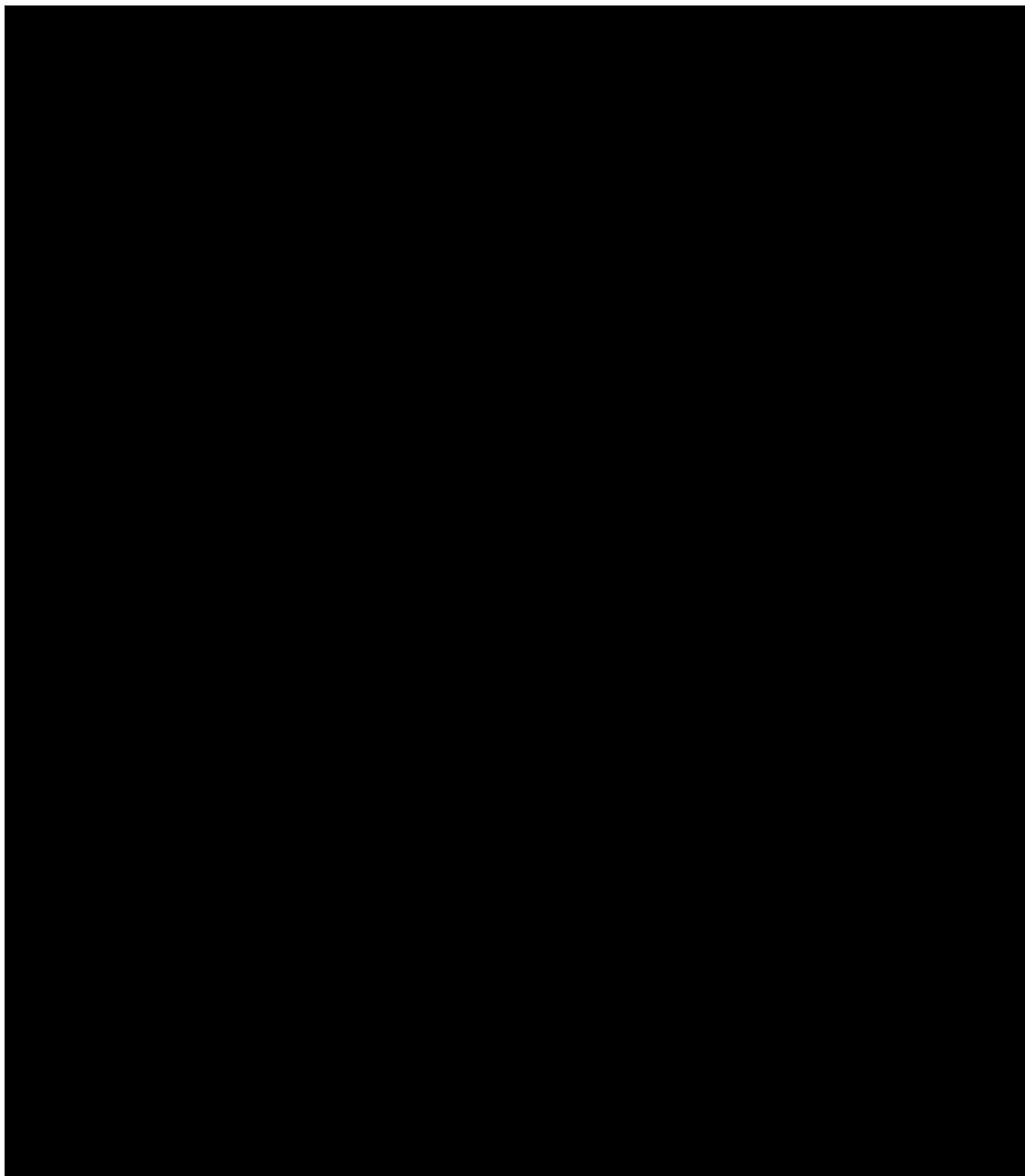
Administration of study treatment will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see [Appendix 7](#).

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**

Tiragolumab or placebo will be administered by IV infusion at a fixed dose of 840 mg together with 1680 mg of atezolizumab ■■■■■ on Day 1 of each 28-day cycle. Tiragolumab/*atezolizumab* and placebo/*atezolizumab* ■■■■■ will be administered per the instructions outlined in [Table 4](#).

**Table 4 Administration of First and Subsequent Infusions of Atezolizumab, or Atezolizumab [REDACTED] Tiragolumab/Placebo**



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 *was originally designed as* 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.

[REDACTED] Eligible participants will be randomized in a 1:1 ratio to receive either tiragolumab plus atezolizumab or placebo plus atezolizumab. [REDACTED]

Eligible participants will be stratified by tumor histology (squamous vs. non-squamous), disease stage (Stage IIB vs. Stage IIIA+ select IIIB [T3N2]), and PD-L1 status [REDACTED]

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**

*Originally*, 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.

*After the Sponsor's decision to phase out the study, the Sponsor and its agents, study site personnel, and participants will be unblinded 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.

Details 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:

[https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy\\_continued\\_access\\_to\\_investigational\\_medicines.pdf](https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/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:

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

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

[REDACTED]

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 Sections 6.8.2 and 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<sub>2</sub>-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  $\beta_2$ -adrenergic agonists).

## **6.8.2            Cautionary Therapy**

### **6.8.2.1        Corticosteroids, Immunosuppressive Medications, and TNF- $\alpha$ Inhibitors**

Systemic corticosteroids, immunosuppressive medications, and TNF- $\alpha$  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- $\alpha$  inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF- $\alpha$  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:

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

## 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 *the investigator determines* may jeopardize the participant's safety if *the participant* continues study treatment
- Investigator 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.

## **7.2 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.

## **7.3 PARTICIPANTS LOST TO FOLLOW-UP**

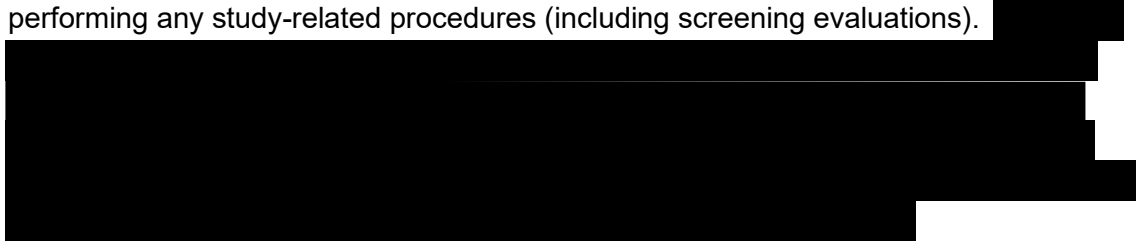
A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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.

## **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).

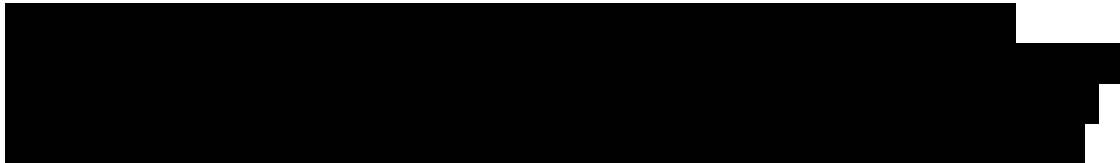


Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

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.



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**

*Following the Sponsor's decision to phase out the study, efficacy assessments will not be performed.*

*To meet eligibility criteria, screening 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 a 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 /CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan. *All disease assessments following the screening assessment will be conducted as per local standard practice to monitor for disease recurrence during the study treatment period. Disease assessments should continue until disease recurrence, withdrawal of consent, death, of study termination by Sponsor, whichever occurs first.*

### **8.1.2      Clinical Outcome Assessments**

*Following the Sponsor's decision to phase out the study, patient-reported outcome assessments will no longer be performed.*

## **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. 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](#).

## **8.3 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 7).

### **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 *treatment*, serious adverse events caused by a protocol-mandated intervention (e.g. *discontinuation of medications*) and/or serious adverse events considered related to the [REDACTED] should be reported *immediately (i.e., no more than 24 hours after the investigator becomes aware of the event)*. In addition, during this period, non-serious adverse events considered related to the [REDACTED] [REDACTED] should be reported within [REDACTED] days after the investigator becomes aware of the event (see Section [A3-5](#)). All other medical events occurring in

*participants during this period are considered preexisting medical conditions and should be recorded as described in Section [A3-7.8](#).*

All adverse events will be reported from the start of treatment until [REDACTED] days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section [1.3](#)), [REDACTED]. All serious adverse events will be collected and followed until [REDACTED] days after the final dose of study treatment [REDACTED]. In addition, adverse events of special interest will continue to be reported until [REDACTED] days after the final dose of study treatment, [REDACTED].

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. *Non-serious adverse events considered related to the [REDACTED] will be reported within [REDACTED] days after the investigator becomes aware of the event.*

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.

*The investigator will be informed of any device deficiencies detected at the testing site that might have an impact on clinical study participants (e.g., a test result leading to inappropriate participant management decision). This will enable the investigator to assess for and report any adverse events associated with the device deficiency (see [Appendix 3](#)).*

### **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 7.2), 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 regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements *for expedited* safety reporting to regulatory *authorities (which includes the use of applicable systems, such as EudraVigilance)*, 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 [REDACTED] days after the final dose of study treatment [REDACTED]. 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 ICF 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 ICF 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**

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:

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

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

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**

*Following the Sponsor's decision to phase out the study, pharmacokinetic assessments are not evaluated in this study.*

## **8.5 PHARMACODYNAMICS**

*Following the Sponsor's decision to phase out the study, pharmacodynamic biomarker assessments will not be performed in this study.*

## **8.6 GENETICS**

Genetic biomarker assessments will *only be performed at participating sites as outlined in Section [8.10.1](#)*.

Refer to Section [8.7](#) for information on genetic biomarkers.

## 8.7 BIOMARKER ASSESSMENTS

*Following the Sponsor's decision to phase out the study, biomarker samples will not be collected, with the exception of required biomarkers listed in the inclusion/exclusion criteria in Sections 5.1 and 5.2, respectively.*

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.

[REDACTED]

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

[REDACTED]

[REDACTED]

However, the storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

*For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report, whichever occurs first. For individuals who are not enrolled (screen failed), remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.*

## **8.8 IMMUNOGENICITY ASSESSMENTS**

*Following the Sponsor's decision to phase out the study, immunogenicity assessments will not be performed in this study.*

## **8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION**

*Following the Sponsor's decision to phase out the study, health economics and medical resource utilization assessments will not be performed in this study.*

## **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 *that were* collected for DNA extraction *under the previous version of this protocol may be used to enable* [REDACTED] [REDACTED] 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 *may* include exploration of germline variants.

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

[REDACTED] 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 [REDACTED] [REDACTED], this section of the protocol (Section 8.10.1) will not be applicable at that site.

[REDACTED]

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

[REDACTED] However, the storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

[REDACTED] Thus, there will be no identification and reporting of incidental findings to investigators or participants.

[REDACTED] 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](mailto: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 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 ICF 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:

- [REDACTED]
- [REDACTED]

The above samples may be sent to one or more laboratories for analysis of germline variants via [REDACTED], or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. [REDACTED] provide a comprehensive characterization of the [REDACTED], 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 ICF 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 ICF (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, [REDACTED]  
[REDACTED].

[REDACTED] 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 ICF 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.

#### **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 ICF. 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 HYPOTHESIS**

*Following the Sponsor's decision to phase out the study, no formal statistical hypothesis will be tested for this study.*

#### **9.2              ANALYSIS SETS**

The participant analysis sets for the purposes of analyses are defined in [Table 5](#).

**Table 5 Participant Analysis Sets**

| Participant Analysis Set | Description  |
|--------------------------|--|
| SAS                      | All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received. |

SAS=safety analysis set.

## 9.3 STATISTICAL ANALYSES

*As a result of the decision to phase out the study, no statistical analysis plan (SAP) will be provided for the study.*

### 9.3.1 General Considerations

All safety analyses will be performed on the SAS.

### 9.3.2 Estimation Methods for the Primary Endpoint

The *original* primary objective for this study *was* 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) [REDACTED] NSCLC who have received adjuvant platinum-based chemotherapy. The *original* primary endpoints *were* investigator-assessed DFS in the [REDACTED]. *After the Sponsor's decision to phase out the study, the primary objective for this study is to evaluate the single safety objective.*

#### 9.3.2.1 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, and changes in laboratory test results.

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. [REDACTED]

[REDACTED] 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.

### **9.3.3            Other Analyses**

#### **9.3.3.1        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 *provided* by treatment arm.

#### **9.3.3.2        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.

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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.

## **Appendix 1: Regulatory, Ethical, and Study Oversight Considerations**

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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., biomarker analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

### **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).

## **Appendix 1: Regulatory, Ethical, and Study Oversight Considerations**

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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.

## **Appendix 1: Regulatory, Ethical, and Study Oversight Considerations**

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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

## **Appendix 1: Regulatory, Ethical, and Study Oversight Considerations**

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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  |
|---|
| <ul style="list-style-type: none"> <li>Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)</li> <li>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, [REDACTED], and lactate dehydrogenase</li> <li>Coagulation: INR and aPTT</li> <li>Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4</li> <li>[REDACTED]</li> <li>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.</li> <li>Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)</li> </ul> |

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.

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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#### 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.

### Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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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

- *Medically significant:*

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 Case 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 (*v5*) 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.

### Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

**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 <sup>a</sup>  |
| 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 <sup>b, c</sup> |
| 4     | Life-threatening consequences or urgent intervention indicated <sup>d</sup>  |
| 5     | Death related to adverse event <sup>d</sup>  |

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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

- <sup>a</sup> Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> 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.

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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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

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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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, serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) *and serious adverse events considered related to the*

**should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) using the Screening Adverse Event eCRF or using the paper Clinical Trial Adverse Event/Special Situations Form if the electronic data capture (EDC) is not available.**

*In addition, during this period, non-serious adverse events considered related to the*

\_\_\_\_\_ should be reported within █ days after the investigator becomes aware of the event using the Screening Adverse Event eCRF or the paper Investigational Medical Device Adverse Event and Device Deficiency Form if the EDC system is not available.

### A3-5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events, *adverse events of special interest, and non-serious medical device adverse events that are considered related* will be reported until [REDACTED] days after the final dose of study treatment. *For serious adverse events and* adverse events of special interest, 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. *For non-serious medical device adverse events that are considered related to the* [REDACTED]

██████████. Reports will be submitted via the EDC system and will be sent to sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, 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 (all serious adverse events) or Investigational Medical Device Adverse Event and Device Deficiency Form (non-serious investigational medical device related), using the fax

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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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 █ 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 █. 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 (*study drug-related events*) or Investigational Medical Device Adverse Event and Device Deficiency Form (*medical device-related*), 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

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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- 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.

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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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 ( $>3 \times \text{ULN}$ ) in combination with either an elevated total bilirubin ( $>2 \times \text{ULN}$ ) 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  $>3 \times \text{ULN}$  in combination with total bilirubin  $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST  $>3 \times \text{ULN}$  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)

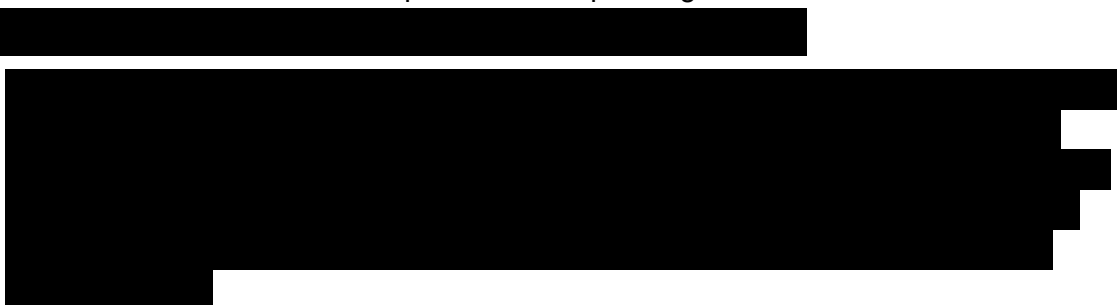
### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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- 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



#### **A3-7.12 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)

### Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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After initiation of study drug, special situations associated with tiragolumab and/or atezolizumab and any associated adverse events will be reported until [REDACTED] days after the final dose of study treatment [REDACTED], and serious adverse events will continue to be reported until [REDACTED] days after the final dose of study treatment [REDACTED]. In addition, adverse events of special interest will continue to be reported until [REDACTED] days after the final dose of study treatment, [REDACTED].

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 [REDACTED] 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 [REDACTED] days after the final dose of study treatment [REDACTED], and serious adverse events will continue to be reported until [REDACTED] days after the final dose of study treatment [REDACTED].

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

### **Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

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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 ■ 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

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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.

Refer to Section 6.1.1 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 7 for guidance on anaphylaxis precautions and Section A4–5.3 for guidance on management of IRRs.

### A4–1.3 LYMPHOPENIA

[REDACTED] in participants treated with tiragolumab, with or without atezolizumab. Participants with a lymphocyte count [REDACTED] 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**

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 [A4-5.3](#) 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.

#### Appendix 4: Safety Plan: Management of Identified and Potential Risks

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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.

[REDACTED]

#### **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 A3-5 for reporting instructions). Adverse events of special interest for this study are as follows:

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

#### Appendix 4: Safety Plan: Management of Identified and Potential Risks

---

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

#### 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 *toxicities* observed with immunomodulatory agents have been mild and self-limiting, *they* 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.

Timely and up-to-date information *the risks associated with atezolizumab should be shared with patients and family caregivers prior to initiating atezolizumab and/or tiragolumab. Patients and caregivers should be instructed to have 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.

- [REDACTED]

## Appendix 4: Safety Plan: Management of Identified and Potential Risks

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

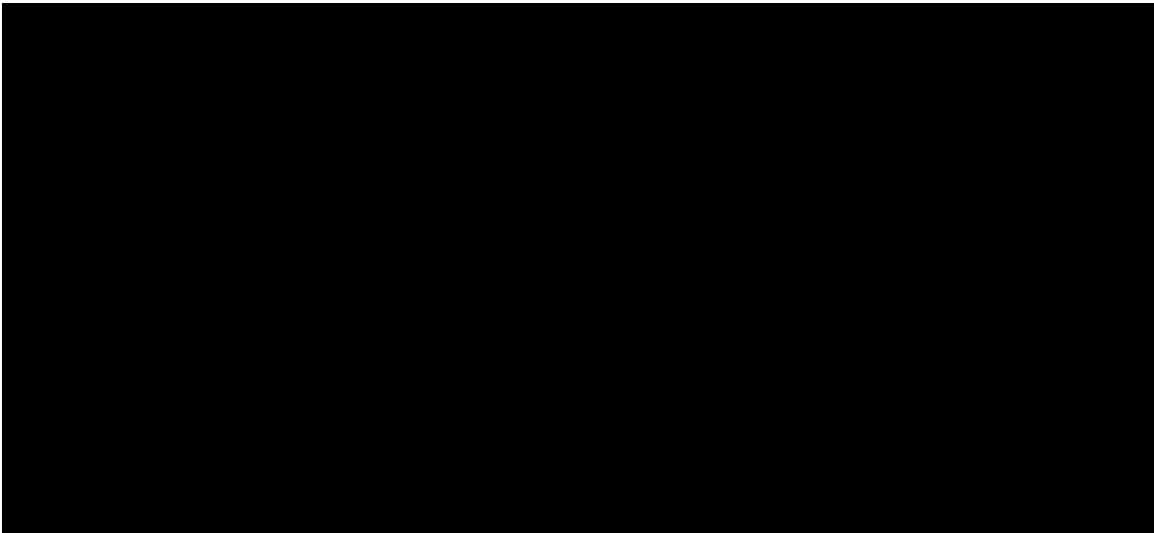
### A4-5.1 DOSE MODIFICATIONS

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.

[REDACTED]



**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 |
|--|------------|
|  |            |

| Event | Management |
|-------|------------|
|-------|------------|

1. *Journal of the American Medical Association*, 2000; 283: 2639-2644.

d

### 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 A4-2](#).

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 A4-2 Management Guidelines for Hepatic Events**

| Event      | Management |
|------------|------------|
| [Redacted] |            |
| a          | [Redacted] |
| b          |            |
| c          |            |

**GASTROINTESTINAL EVENTS**

Management guidelines for diarrhea or colitis are provided in [Table A4-3](#).

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 A4-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)**

| Event | Management |
|-------|------------|
|       |            |

| Event | Management |
|-------|------------|
|-------|------------|

[illegible]

C

**ENDOCRINE EVENTS**

Management guidelines for endocrine events are provided in [Table A4-4](#).

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, adrenocorticotrophic 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 A4-4 Management Guidelines for Endocrine Events**

| Event | Management |
|-------|------------|
|       |            |

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

| Event | Management |
|-------|------------|
|       |            |

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

| Event | Management |
|-------|------------|
|       |            |

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

|   |  |
|---|--|
| a |  |
| b |  |
| c |  |

**OCULAR EVENTS**

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in [Table A4-5](#).

**Table A4-5 Management Guidelines for Ocular Events**

| Event | Management |
|-------|------------|
| a     |            |
|       |            |
|       |            |
| b     |            |
| c     |            |

## **IMMUNE-MEDIATED CARDIAC EVENTS**

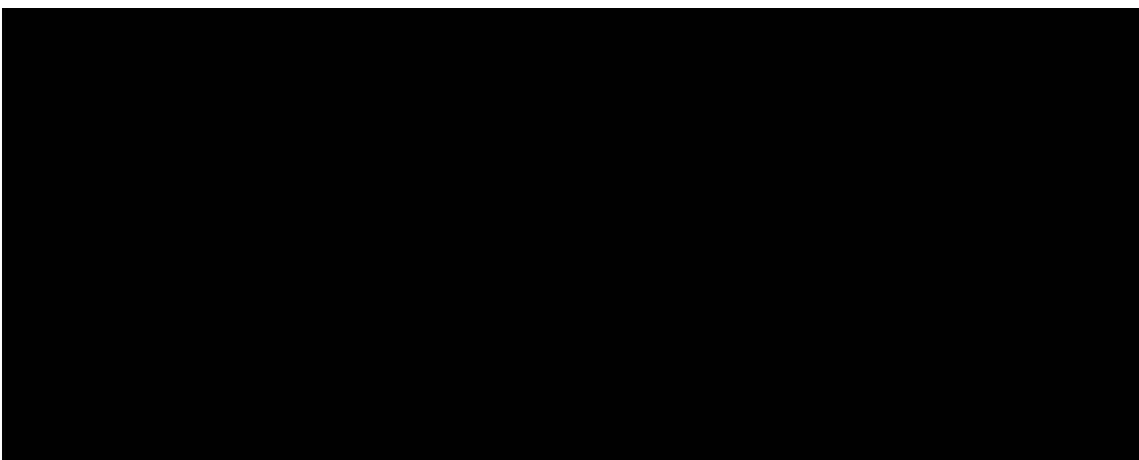


### **IMMUNE-MEDIATED MYOCARDITIS**

*Myocarditis symptoms are nonspecific and may occur as early as days or weeks after the first or second dose of atezolizumab with or without tiragolumab.*

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 associated with pericarditis (see section on immune-mediated pericardial disorders below) and should be managed accordingly. *Although myocarditis events are rare, myocarditis is often severe and associated with myositis or myasthenia gravis.*

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.



Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A4-6](#).

**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).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Table A4-6 Management Guidelines for Immune-Mediated Cardiac Events**

| Event      | Management |
|------------|------------|
| [REDACTED] |            |

**INFUSION-RELATED REACTIONS**



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 A4-7](#).

**Table A4-7 Management Guidelines for Infusion-Related Reactions**

| Event  | Management |
|--|------------|
| A large rectangular area of the document is completely redacted with a solid black fill. |            |

### Table A4-7 Management Guidelines for Infusion-Related Reactions

a

b

#### Appendix 4: Safety Plan: Management of Identified and Potential Risks

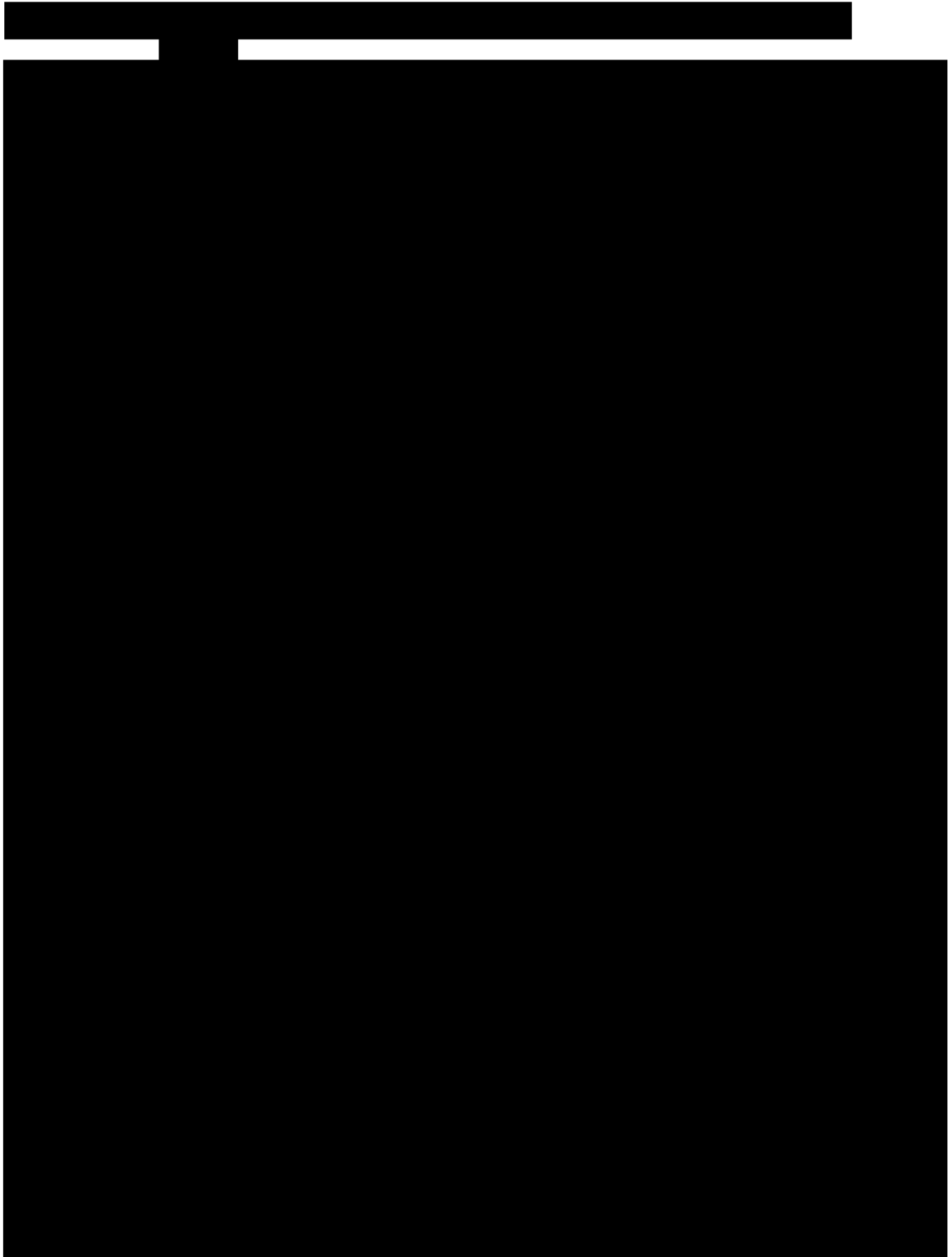
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[REDACTED]

[REDACTED]

#### Appendix 4: Safety Plan: Management of Identified and Potential Risks

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## 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 A4-9](#).

**Table A4-9 Management Guidelines for Pancreatic Events, Including Pancreatitis**

| Event | Management |
|-------|------------|
|       |            |

**Table A4-9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)**

| Event      | Management |
|------------|------------|
| [REDACTED] |            |
| a          | [REDACTED] |
| b          |            |
| c          |            |

**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. [REDACTED]

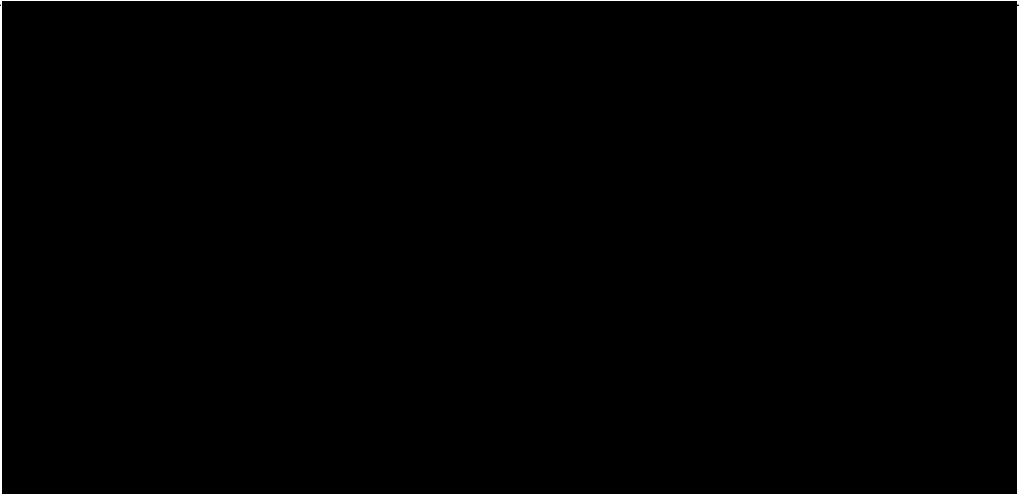
[REDACTED]

Management guidelines for dermatologic events are provided in [Table A4-10](#).

**Table A4-10 Management Guidelines for Dermatologic Events**

| Event | Management |
|-------|------------|
|       |            |

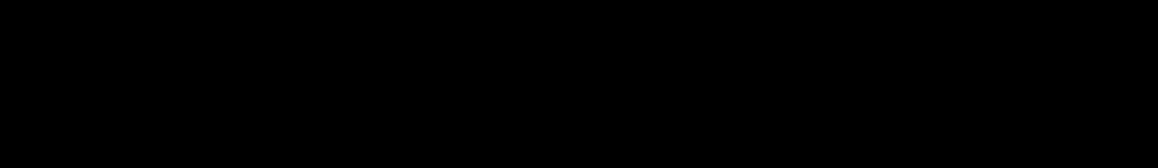
**Table A4-10 Management Guidelines for Dermatologic Events (cont.)**

|   |  |
|---|--|
| a |  |
| b |  |
| c |  |

**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 A4-11](#) with specific guidelines for myelitis provided in [Table A4-12](#).

**Table A4-11 Management Guidelines for Neurologic Disorders**

| Event  | Management |
|--|------------|
|  |            |

**Table A4-11 Management Guidelines for Neurologic Disorders (cont.)**

| Event | Management |
|-------|------------|
|       |            |

Table A4-11 Management Guidelines for Neurologic Disorders (cont.)

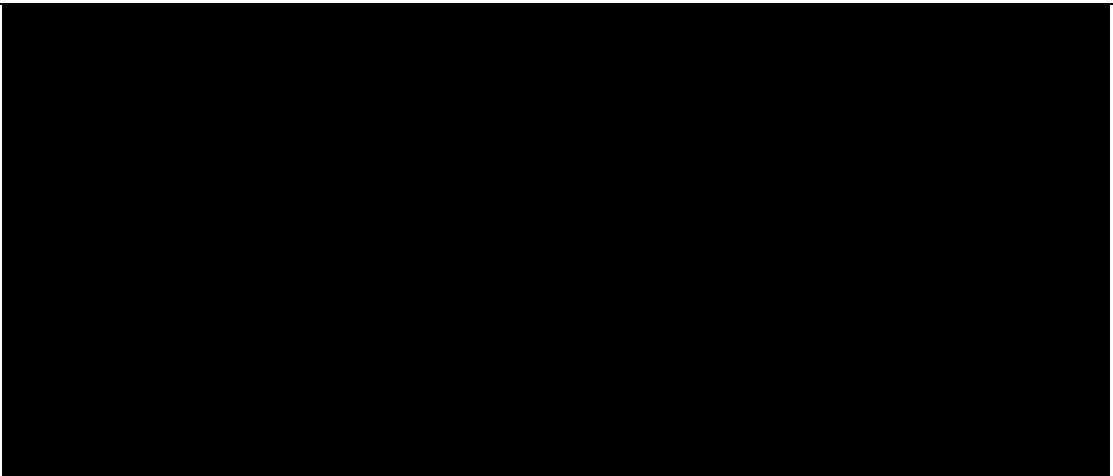
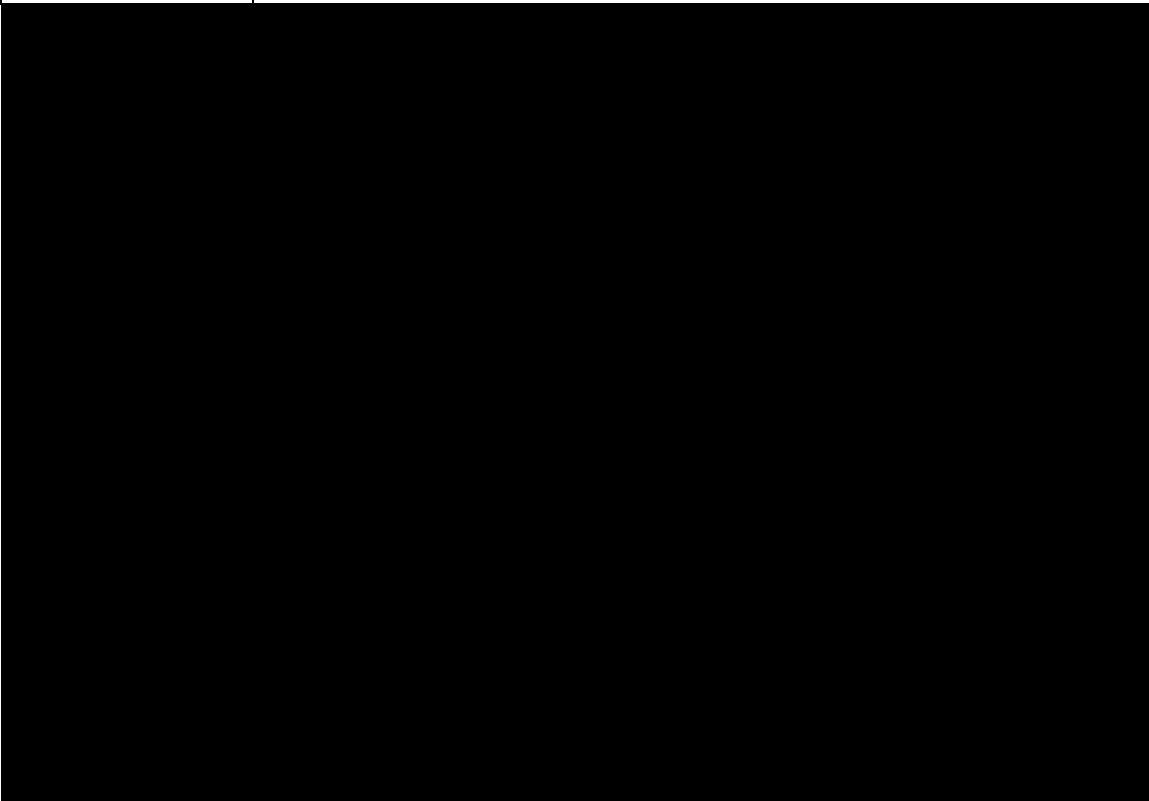
|   |  |
|---|--|
| a |  |
| b |  |
| c |  |

Table A4-12 Management Guidelines for Immune-Mediated Myelitis

| Event   | Management |
|---|------------|
|  |            |

**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.

[REDACTED]

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A4-13](#).

**Table A4-13 Management Guidelines for Immune-Mediated Meningoencephalitis**

| Event      | Management |
|------------|------------|
| [REDACTED] |            |

**RENAL EVENTS**

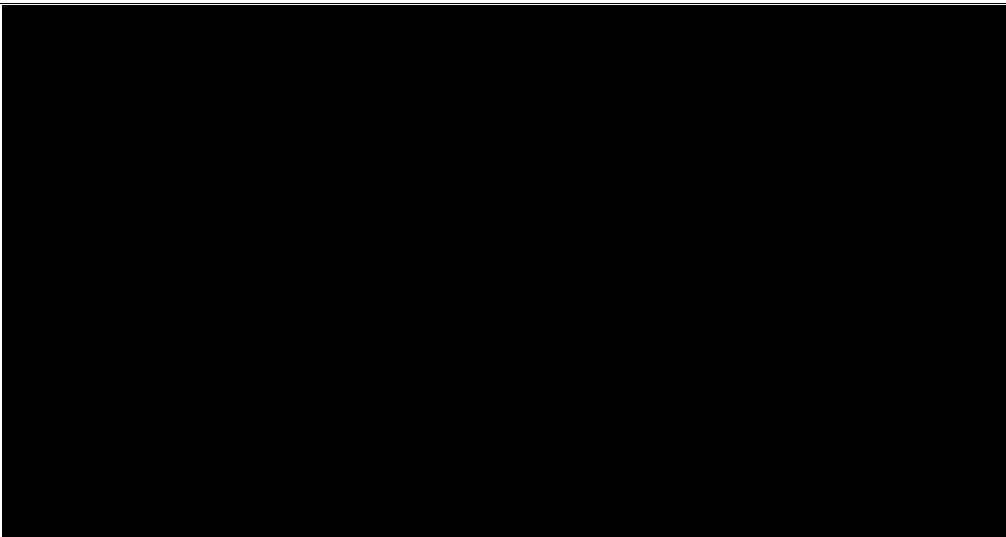
Eligible participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and 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 A4-14](#).

**Table A4-14     Management Guidelines for Renal Events**

| Event | Management |
|-------|------------|
|       |            |

**Table A4-14 Management Guidelines for Renal Events (cont.)**

|   |  |
|---|--|
| a |  |
| b |  |
| c |  |

#### **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.

|  |  |
|--|--|
|  |  |
|--|--|

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in [Table A4-15](#).

**Table A4-15     Management Guidelines for Immune-Mediated Myositis**

| Event | Management |
|-------|------------|
|       |            |



#### Appendix 4: Safety Plan: Management of Identified and Potential Risks

---

[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

## **Appendix 5**

### **Collection of Pregnancy Information**

#### **TABLE OF CONTENTS**

|      |   |     |
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| A5-3 | Abortions .....   | 145 |
| A5-4 | Abnormal Pregnancy Outcomes .....                         | 145 |

### **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 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

## **Appendix 5: Collection of Pregnancy Information**

---

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

### 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.

|  |  |
|--|--|
| <b>T: Primary tumor</b>  |  |
| <b>Tx</b>  | 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  |
| <b>T0</b>  | No evidence of primary tumor   |
| <b>Tis</b>   | Carcinoma in situ  |
| <b>T1</b>  | 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) <sup>a</sup>   |
| <b>T1a(mi)</b>   | Minimally invasive adenocarcinoma <sup>b</sup>   |
| <b>T1a</b>   | Tumor ≤1 cm in greatest dimension <sup>a</sup>   |
| <b>T1b</b>   | Tumor >1 cm but ≤2 cm in greatest dimension <sup>a</sup>   |
| <b>T1c</b>   | Tumor >2 cm but ≤3 cm in greatest dimension <sup>a</sup>   |
| <b>T2</b>  | Tumor >3 cm but ≤5 cm or tumor with any of the following features <sup>c</sup> :<br>- Involves main bronchus regardless of distance from the carina but without involvement of the carina<br>- Invades visceral pleura<br>- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung |
| <b>T2a</b>   | Tumor >3 cm but ≤4 cm in greatest dimension  |
| <b>T2b</b>   | Tumor >4 cm but ≤5 cm in greatest dimension  |
| <b>T3</b>  | 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  |
| <b>T4</b>  | 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                                       |
| <b>N: Regional lymph node involvement</b>  |  |
| <b>Nx</b>  | Regional lymph nodes cannot be assessed  |
| <b>N0</b>  | No regional lymph node metastasis  |
| <b>N1</b>  | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension   |
| <b>N2</b>  | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)  |
| <b>N3</b>  | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)   |
| <b>M: Distant metastasis</b>   |  |
| <b>M0</b>  | No distant metastasis  |
| <b>M1</b>  | Distant metastasis present   |
| <b>M1a</b>   | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion <sup>d</sup>  |
| <b>M1b</b>   | Single extrathoracic metastasis <sup>e</sup>   |
| <b>M1c</b>   | Multiple extrathoracic metastases in one or more organs  |
| <p><b>Note:</b> Changes to the seventh edition are in bold.</p> <p><sup>a</sup>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.</p> <p><sup>b</sup>Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.</p> <p><sup>c</sup>T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if &gt;4 cm but ≤5 cm in greatest dimension.</p> <p><sup>d</sup>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.</p> <p><sup>e</sup>This includes involvement of a single distant (nonregional) lymph node.</p> |  |

## Appendix 6: AAJCC/UICC Non-Small Cell Lung Cancer Staging, 8th Edition

| Descriptor in 7th edition                     | Proposed T/M | N categories  |           |             |             |
|---|--------------|---------------|-----------|-------------|-------------|
|   |              | Overall stage |           |             |             |
|   |              | N0            | N1        | N2          | N3          |
| T1 ≤ 1 cm                                     | T1a          | IA1 (IA)      | IB (IIA)  | IIIA        | IIIB        |
| T1 > 1-2 cm                                   | T1b          | IA2 (IA)      | IB (IIA)  | IIIA        | IIIB        |
| T1 > 2-3 cm                                   | T1c          | IA3 (IA)      | IB (IIA)  | IIIA        | IIIB        |
| T2 > 3-4 cm                                   | T2a          | IB            | IB (IIA)  | IIIA        | IIIB        |
| T2 > 4-5 cm                                   | T2b          | IIA (IB)      | IB (IIA)  | IIIA        | IIIB        |
| T2 > 5-7 cm                                   | T3           | IIIB (IIA)    | IIA (IIB) | IIIB (IIIA) | IIIC (IIIB) |
| T3 structures                                 | T3           | IIIB          | IIA       | IIIB (IIIA) | IIIC (IIIB) |
| T3 > 7 cm                                     | T4           | IIIA (IIB)    | IIA       | IIIB (IIIA) | IIIC (IIIB) |
| T3 diaphragm                                  | T4           | IIIA (IIB)    | IIA       | IIIB (IIIA) | IIIC (IIIB) |
| T3 endobronchial: location/atelectasis 3-4 cm | T2a          | IB (IIB)      | IB (IIIA) | IIIA        | IIIB        |
| T3 endobronchial: location/atelectasis 4-5 cm | T2b          | IIA (IIB)     | IB (IIIA) | IIIA        | IIIB        |
| T4  | T4           | IIIA          | IIA       | 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)    |

<sup>a</sup>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 7**

### **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 8**

### **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 9

### Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

**Table A9-1 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) <sup>a</sup> | Authorized                            | No <sup>b</sup>                     |
| Tiragolumab placebo      | IMP (placebo)                   | Unauthorized                          | Not applicable                      |

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

<sup>a</sup> Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

<sup>b</sup> Atezolizumab monotherapy is approved as adjuvant treatment for participants with PD-L1 high ( $\geq 50\%$  TC) NSCLC.

**Table A9-2 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) <sup>a</sup> | Authorized                           | No <sup>b</sup>                     |
| Tiragolumab placebo      | IMP (placebo)                   | Unauthorized                         | Not applicable                      |

AxMP = auxiliary medicinal product; IMP = investigational medicinal product; UK = United Kingdom.

<sup>a</sup> Atezolizumab is considered to be an IMP test product as well as an IMP comparator.

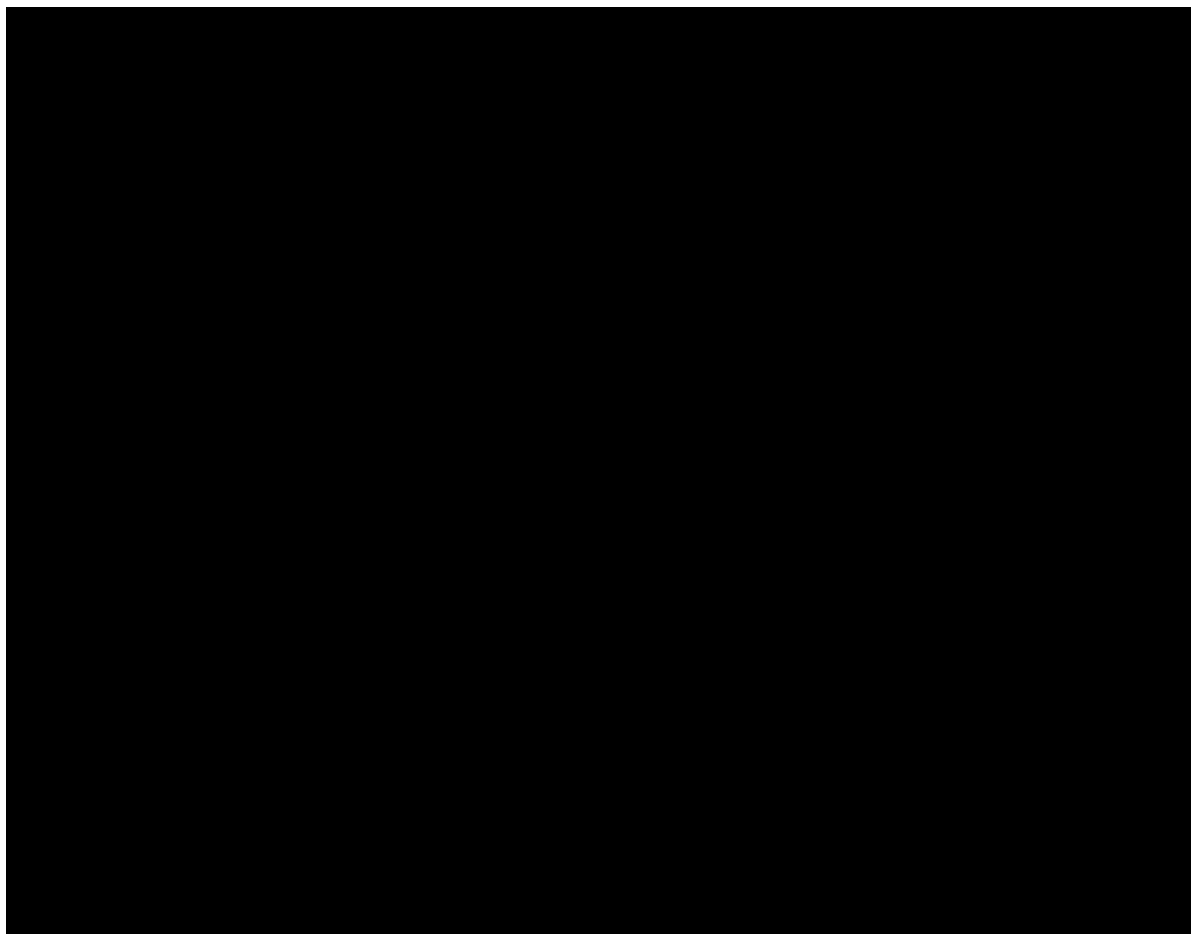
<sup>b</sup> Atezolizumab monotherapy is approved as adjuvant treatment for participants with PD-L1 high ( $\geq 50\%$  TC) NSCLC.

## **Appendix 10**

### **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**



## **Appendix 11**

### **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<sup>2</sup> Day 1, Pemetrexed 500 mg/m<sup>2</sup> Day 1 every 21 days for 4 cycles

#### **Preferred (squamous)**

- Cisplatin 75 mg/m<sup>2</sup> Day 1, Gemcitabine 1250 mg/m<sup>2</sup> Days 1 and 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m<sup>2</sup> day 1, Docetaxel 75 mg/m<sup>2</sup> day 1 every 21 days for 4 cycles

#### **Other Recommended**

- Cisplatin 50 mg/m<sup>2</sup> days 1 and 8, Vinorelbine 25 mg/m<sup>2</sup> days 1, 8, 15, and 22, every 28 days for 4 cycles
- Cisplatin 100 mg/m<sup>2</sup> day 1, Vinorelbine 30 mg/m<sup>2</sup> days 1, 8, 15, and 22, every 28 days for 4 cycles
- Cisplatin 75–80 mg/m<sup>2</sup> day 1, Vinorelbine 25–30 mg/m<sup>2</sup> days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m<sup>2</sup> day 1, Etoposide 100 mg/m<sup>2</sup> 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<sup>2</sup> day 1, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, Gemcitabine 1000 mg/m<sup>2</sup> days 1 and 8, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, Pemetrexed 500 mg/m<sup>2</sup> day 1 every 21 days for 4 cycles (nonsquamous histology)

*Appendix 12*  
***Entity for Testing, Analysis, and Biosample Destruction in China***

*The Sponsor delegates the testing, analysis, and destruction of samples for Study GO45006 from China sites to the following China domestic companies.*

| <b><i>Laboratory for Testing and Analysis</i></b>                | <b><i>Biosample Destruction Provider</i></b>                        |
|--|---|
| <i>HistoGeneX Medical Science and Technology (Shandong) Ltd.</i> | <i>Jining Yuandong Ecological Environmental Protection Co. Ltd.</i> |

## Appendix 13 Abbreviations

| Abbreviation or Term | Definition                                     |
|----------------------|--|
| ADA                  | anti-drug antibody                             |
| ALK                  | anaplastic lymphoma kinase                     |
| BEN                  | benign ethnic neutropenia                      |
| BSC                  | best supportive care                           |
| CDx                  | Companion Diagnostics                          |
| CFR                  | Code of Federal Regulations                    |
| CIT                  | cancer immunotherapy                           |
| COPD                 | chronic obstructive pulmonary disease          |
| COVID-19             | Coronavirus 2019                               |
| CPI                  | checkpoint inhibitor                           |
| CRF                  | case report form                               |
| CRS                  | cytokine release syndrome                      |
| CT                   | computed tomography                            |
| CTCAE                | Common Terminology Criteria for Adverse Events |
| DFS                  | disease-free survival                          |
|                      |  |
| EC                   | Ethics Committee                               |
| ECOG                 | Eastern Cooperative Oncology Group             |
| eCRF                 | electronic case report Form                    |
| EDC                  | electronic data capture                        |
| EFS                  | event free survival                            |
| <i>EGFR</i>          | epidermal growth factor receptor               |
| Fc                   | fragment crystallizable                        |
| FDA                  | Food and Drug Administration                   |
| FFPE                 | formalin-fixed, paraffin-embedded              |
|                      |  |
| HR                   | hazard ratio                                   |
| ICF                  | Informed Consent Form                          |
| IFN                  | interferon                                     |
| IL                   | interleukin                                    |
| IMP                  | investigational medicinal product              |
| IRB                  | Institutional Review Board                     |

## Appendix 13: Abbreviations

| Abbreviation or Term | Definition                                      |
|----------------------|---|
| IRR                  | infusion-related reaction                       |
| ITT                  | intent-to-treat                                 |
| IxRS                 | interactive voice or web-based response system  |
| mAb                  | monoclonal antibody                             |
| MLND                 | mediastinal lymph node dissection               |
| MRI                  | magnetic resonance imaging                      |
| MTD                  | maximum tolerated dose                          |
| NCCN                 | National Comprehensive Cancer Network           |
| NCI                  | National Cancer Institute                       |
| NK                   | natural killer                                  |
| NSCLC                | non-small cell lung cancer                      |
| ORR                  | objective response rate                         |
| OS                   | overall survival                                |
| PBS                  | Pharma Biosample Services                       |
| pCR                  | pathological complete response                  |
| PCR                  | polymerase chain reaction                       |
| PFS                  | progression-free survival                       |
| PK                   | pharmacokinetic                                 |
| PORT                 | postoperative radiotherapy                      |
| PVR                  | poliovirus receptor                             |
| Q3W                  | every 3 weeks                                   |
| Q4W                  | every 4 weeks                                   |
| RBR                  | Research Biosample Repository                   |
| RT                   | radiotherapy                                    |
| SARS-CoV-2           | severe acute respiratory syndrome coronavirus 2 |
| SOC                  | standard of care                                |
| TC                   | tumor cell                                      |
| TIGIT                | T-cell immunoreceptor with Ig and ITIM domains  |
| TNF- $\alpha$        | tumor necrosis factor- $\alpha$                 |
| TPS                  | tumor proportion score                          |
| ULN                  | upper limit of normal                           |
|                      |   |

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