Official Title: A Phase II, Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Neoadjuvant and Adjuvant Tiragolumab Plus Atezolizumab, With or Without Platinum-Based Chemotherapy, in Patients With Previously Untreated Locally Advanced Resectable Stage II, IIIA, or Select IIIB Non–Small Cell Lung Cancer

NCT Number: NCT04832854

Document Date: Protocol Amendment Version 5: 19-December-2023

PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF NEOADJUVANT AND ADJUVANT TIRAGOLUMAB PLUS ATEZOLIZUMAB, WITH OR WITHOUT PLATINUM-BASED CHEMOTHERAPY, IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO42501
VERSION NUMBER:	5
REGULATORY AGENCY IDENTIFIERS:	EudraCT NUMBER: 2020-002853-11 EU CT NUMBER: 2022-502978-17-00 IND NUMBER: 129,258 NCT NUMBER: NCT04832854
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann–La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL	See electronic signature and date stamp on final page of this document

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on the final page of this document.
4	20 December 2022
3	2 February 2022
2	23 February 2021
1	19 August 2020

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol GO42501 has been amended to align with [redacted]. In addition, risks and management guidelines for atezolizumab have been updated to align with the latest Atezolizumab Investigator's Brochure ([IB] Version 20). Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- Cohort A, which was designed for the combination treatment of tiragolumab and atezolizumab for patients with at least [redacted], has been closed early due to the changing treatment landscape which includes chemotherapy as part of the approved treatment regimen in the perioperative setting (Section 1.3 and Section 3.1.1.1, Figure 2, Section 6.1, Section 6.5).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.4).
- The analysis for the pathological response has changed from central to local pathology laboratory since all local pathologists were trained to follow the assessment guidance per the pathology manual and [redacted] endpoints associated with central pathological review are removed (Section 2, Table 2, Section 3.1.1, Section 3.4.3, Section 4.5.7, Section 6.5.3).
- The chemotherapy regimen cisplatin + gemcitabine has been removed as an option from the protocol as no patients have been dosed with this regimen in this study (Sections 3.1.1, Section 4.3.2, Section 4.3.2.4, Appendix 1, Appendix 11).
- Clarification has been made that the last joint monitoring committee (JMC) meeting will be conducted after the last patient completes surgery. However, the JMC chair and medical monitor can request an ad-hoc JMC if any potential safety concerns need further investigation (Section 3.1.2).
- Event-free survival (EFS) definition was updated to align to the FDA guidance (Section 2, Section 6.5.2)
- The post-surgery visit row of Appendix 2 that was mistakenly deleted due to formatting error has been added back in.
- Adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 12) and updated SmPCs of chemotherapies.
- Additional changes have been made to align with the EU Clinical Trial Regulation (CTR):
  - Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1).
  - The synopsis has been simplified.

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

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF NEOADJUVANT AND ADJUVANT TIRAGOLUMAB PLUS ATEZOLIZUMAB, WITH OR WITHOUT PLATINUM-BASED CHEMOTHERAPY, IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO42501
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SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann–La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland

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

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF NEOADJUVANT AND ADJUVANT TIRAGOLUMAB PLUS ATEZOLIZUMAB, WITH OR WITHOUT PLATINUM-BASED CHEMOTHERAPY, IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON-SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	EudraCT Number: 2020-002853-11 EU CT Number: 2022-502978-17-00 IND Number: 129,258 NCT Number: NCT04832854

STUDY RATIONALE

In light of the evidence of clinical activity of atezolizumab plus tiragolumab in NSCLC and the need to improve survival and decrease recurrence rates for patients with resectable early-stage NSCLC, the Sponsor is conducting this Phase II study. This study will evaluate the surgical safety and feasibility of atezolizumab plus tiragolumab alone (Atezo + Tira) or in combination with platinum-based chemotherapy (Atezo + Tira + Chemo) as neoadjuvant treatment for patients with previously-untreated locally advanced non-small cell lung cancer (NSCLC). The study will also evaluate the efficacy, pharmacokinetics, immunogenicity, and safety of neoadjuvant Atezo + Tira or Atezo + Tira + Chemo, followed by adjuvant Atezo + Tira or adjuvant platinum-based chemotherapy.

OBJECTIVES AND ENDPOINTS

Primary Safety Objectives	*Corresponding Endpoints*
• *To evaluate the safety of Atezo + Tira as neoadjuvant treatment followed by either Atezo + Tira or chemo as adjuvant treatment* • *To evaluate the safety of Atezo + Tira + Chemo as neoadjuvant treatment followed by Atezo + Tira as adjuvant treatment*	• *Incidence and length of surgical delays, incidence of operative and post-operative complications, and/or number of surgical cancellations related to study treatment* • *Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0* [redacted]
Primary Efficacy Objective	*Corresponding Endpoint*
• *To evaluate the efficacy of Atezo + Tira or Atezo + Tira + Chemo as neoadjuvant treatment*	• *MPR rate, defined as the proportion of patients who achieve MPR, with MPR, defined as ≤10% residual viable tumor at the time of surgical resection in the primary tumor, as assessed by the local pathology laboratory*
Secondary Efficacy Objectives	*Corresponding Endpoints*

• *To evaluate the efficacy of Atezo + Tira or Atezo + Tira + Chemo as neoadjuvant treatment* • *To evaluate the efficacy of Atezo + Tira as neoadjuvant treatment followed by either Atezo + Tira or chemotherapy as adjuvant treatment* • *To evaluate the efficacy of Atezo + Tira + Chemo as neoadjuvant treatment followed by Atezo + Tira as adjuvant treatment*	• *pCR, defined as the absence of any viable tumor cells in both the primary tumor and all sampled lymph nodes at the time of surgical resection, as assessed by the local pathology laboratory* • *EFS, defined as the time from first dose of study drug to any of the following events, whichever occurs first: disease progression that precludes surgical resection, as assessed by the investigator, or local or distant disease recurrence after surgery, including the occurrence of a new primary NSCLC, or death from any cause*

ADA = anti-drug antibody; [redacted] *Atezo + Tira = atezolizumab plus tiragolumab; Atezo + Tira + Chemo = atezolizumab plus tiragolumab plus platinum-based chemotherapy; CRS = cytokine-release syndrome; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; MPR = major pathological response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NSCLC = non-small cell lung cancer; pCR = pathological complete response;.*

OVERALL DESIGN AND STUDY POPULATION

This is a global Phase II, open-label, multicenter study evaluating the safety and efficacy of neoadjuvant and adjuvant atezolizumab plus tiragolumab, with or without platinum-based chemotherapy, in patients with previously untreated, histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC.

This study is designed to establish proof-of-concept clinical data that neoadjuvant treatment with Atezo + Tira or Atezo + Tira + Chemo is safe, tolerable and does not have a clinically significant negative effect on surgical outcomes in patients with early-stage resectable NSCLC. This study is also designed to evaluate potential anti-tumor effects of neoadjuvant Atezo + Tira or Atezo + Tira + Chemo, as measured by major pathological response (MPR). The study is designed with the flexibility to open new cohorts as new treatment combinations become available.

Patients will be assigned to a cohort on the basis of PD-L1 status (see below) and will receive treatment as follows:

- ***Cohort A (PD-L1 high)**: neoadjuvant Atezo + Tira for 4 cycles, followed by surgical resection and either adjuvant Atezo + Tira for 16 cycles or adjuvant chemotherapy for 4 cycles*
- ***Cohort B (PD-L1 all comers)**: neoadjuvant Atezo + Tira + Chemo for 4 cycles, followed by surgical resection and adjuvant Atezo + Tira for 16 cycles*

Selection of the platinum-based chemotherapy regimen will be at the discretion of the investigator, based on histology subtypes and documented at the time of initiation. The following platinum-based chemotherapy options are permitted for this study.

For Non-squamous NSCLC	*For Squamous NSCLC*
Cisplatin + pemetrexed *Carboplatin + pemetrexed* *Carboplatin + paclitaxel*	*Carboplatin + gemcitabine* *Carboplatin + paclitaxel*

NSCLC = non-small cell lung cancer.

Surgical specimens will be assessed for pathological response (MPR and pathological complete response [pCR]) by an independent central pathology laboratory as well as by the investigator's site pathology laboratory. In addition, exploratory biomarker analyses will be performed on remaining FFPE tissue (primary tumor tissue and dissected lymph nodes) post MPR assessment.

Postoperative radiotherapy (PORT) will be allowed for patients with confirmed, pathological N2 + disease or positive tumor margins present at the time of surgical resection (ypN2 and/or R1/R2) and must be administered prior to adjuvant Atezo + Tira treatment or after adjuvant platinum-based chemotherapy.

Patients must be eligible for R0 resection with curative intent at screening and must meet all eligibility criteria. Patients who do not meet the criteria for participation in this study (screen failures) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. The investigator will record reasons for screen failure in the screening log.

Treatment Assignment and Safety Lead-In Based on Tumor PD-L1 Status

After providing informed consent, patients will undergo screening procedures, including central assessment of PD-L1 status by [redacted]. *High PD-L1 expression is defined as* [redacted] *of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control. Enrollment will be completed in a stepwise manner as follows, with approximately* [redacted] *patients enrolled in each of the cohorts. Cohort A enrollment was closed in September 2023:*

- *Initially there will be a safety lead-in:*
  - [redacted]
  - [redacted]
- *The Joint Monitoring Committee (JMC) will evaluate the safety of each cohort, and if deemed to be safe:*
  - [redacted]
  - [redacted]
- [redacted]

Safety Lead-In

To account for potential surgical delays, cancellations or complications related to study treatment, enrollment within each cohort will be suspended to allow for a safety evaluation after approximately 6 patients have completed neoadjuvant treatment and either completed surgery or had their surgery plan changed. The cohorts may not enroll at the same speed, and each cohort will be evaluated separately and independently. The safety evaluation will be based on safety and surgical data and reviewed by the JMC, who will recommend either continuing enrollment into that cohort or closing the cohort. During this safety lead-in period, a patient may be replaced if he or she does not proceed to surgery for reasons other than an adverse event of special interest or disease progression.

[redacted]

[redacted]

Surgery and Adjuvant Treatment

Patients will undergo surgical resection of their tumor upon completion of four cycles of neoadjuvant therapy. Prior to the surgery, the attending surgeon and medical oncologist will reassess the patient.

The pre-surgery visit should occur within 30 days after the last dose of neoadjuvant treatment; repeat pulmonary function tests (PFTs) (if clinically indicated), as well as associated assessments should be performed in accordance with local institutional practice. The surgical procedure should be performed within 30 days after the pre-surgery visit if judged clinically feasible by both the attending surgeon and medical oncologist. Surgical data should be entered on the corresponding electronic Case Report Form (eCRF) as soon as possible after surgery, especially during the safety lead-in, so that assessment of surgical delays, cancellations, or complications can be completed in a timely manner.

Patients who are found to have disease progression at scheduled tumor assessments (after Cycle 2 and Cycle 4) or at any time during neoadjuvant treatment and are still deemed resectable and non-metastatic will proceed to surgery if amenable and will remain eligible for all study treatment and evaluations.

Patients who discontinue neoadjuvant treatment early because of disease progression and do not proceed to surgery will be discontinued from additional clinic study procedures and will proceed to receive other treatment as determined by the investigator. Such patients will remain in the study for survival follow-up. For patients who are responding to neoadjuvant therapy but cannot proceed to surgery due to an unforeseen medical issue (e.g., pulmonary embolism or myocardial infarction), and the patient can continue protocol-specified treatment, such as chemotherapy (Cohort A [PD-L1 high]) or Atezo + Tira (Cohort A or B) and radiotherapy.

After surgical resection, patients will continue to receive adjuvant Atezo + Tira or adjuvant chemotherapy (Cohort A [PD-L1 high] only) until one of the following occurs: administration of up to four cycles of adjuvant chemotherapy per local standard of care, 16 cycles of adjuvant Atezo + Tira, unacceptable toxicity, disease recurrence, death, or patient and/or physician decision to discontinue study treatment.

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

Phase:	*II*	***Population Type:***	*Adult patients*
Control Method:	*None*	***Population Diagnosis or Condition:***	*Stage II–Select stage IIIB NSCLC*
Interventional Model:	*Parallel group*	***Population Age:***	*≥18 years*
Test Compound{s}:	*Atezolizumab plus tiragolumab*	***Site Distribution:***	*Multisite*
Active Comparator:	*None*	***Study Intervention Assignment Method:***	*Assigned*
Number of Cohorts:	*2*	***Number of Participants to Be Enrolled:***	*Approximately 50*

STUDY TREATMENT

Patients will be assigned to a cohort on the basis of PD-L1 status (see below) and will receive treatment as follows:

- ***Cohort A (PD-L1 high)**: neoadjuvant Atezo + Tira for 4 cycles, followed by surgical resection and either adjuvant Atezo + Tira for 16 cycles or adjuvant chemotherapy for 4 cycles*
- ***Cohort B (PD-L1 all comers)**: neoadjuvant Atezo + Tira + Chemo for 4 cycles, followed by surgical resection and adjuvant Atezo + Tira for 16 cycles*

Selection of the platinum-based chemotherapy regimen will be at the discretion of the investigator, based on histology subtypes and documented at the time of initiation. The following platinum-based chemotherapy options are permitted for this study.

For Non-squamous NSCLC	*For Squamous NSCLC*
Cisplatin + pemetrexed *Carboplatin + pemetrexed* *Carboplatin + paclitaxel*	*Carboplatin + gemcitabine* *Carboplatin + paclitaxel*

DURATION OF PARTICIPATION

The total duration of study participation for each individual from screening until completion may vary. The total duration of study participation for each individual is expected to range from 1 day to more than 5 years.

COMMITTEES

Independent Committees:	*Not applicable*
Other Committees:	*Joint Monitoring Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell cytotoxicity
ALK	anaplastic lymphoma kinase
[redacted]	
Atezo	atezolizumab
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
CAP	College of American Pathologists
[redacted]	
CE	Conformitè Europëenne
Chemo	platinum-based chemotherapy
CIT	cancer immunotherapy
CLIA	Clinical Laboratory Improvement Amendments
COPD	chronic obstructive pulmonary disease
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DFS	disease-free survival
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EAE	experimental autoimmune encephalitis
EBUS	endobronchial ultrasound
EBUS TBNA	EBUS-guided transbronchial needle aspirations
[redacted]	
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	Event free survival
EGFR	epidermal growth factor receptor

Abbreviation	Definition
EORTC	European Organisation for Research and Treatment of Cancer
EUS	endoscopic ultrasound
EUS-FNA	EUS-guided fine-needle aspirations
Fc	fragment crystallizable
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
GFR	glomerular filtration rate
GGO	ground-glass opacity
GHS	global health status
Gy	grays
[redacted]	
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IFN-γ	interferon-γ
IHC	immunohistochemistry
IL	interleukin
IL	Item List
[redacted]	
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
JMC	joint monitoring committee
LACE	Lung Adjuvant Cisplatin Evaluation
mAb	monoclonal antibody
MAS	macrophage activation syndrome

Abbreviation	Definition
MPR	major pathological response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	nivolimab
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NI	nivolimab and ipilimumab
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
pCR	pathological complete response
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PK	pharmacokinetic
ppo	predicted postoperative
PORT	postoperative radiotherapy
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
PVR	poliovirus receptor
Q3W	every 3 weeks
[redacted]	
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros proto-oncogene 1, receptor tyrosine kinase
SCLC	small cell lung cancer
SOC	standard of care
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tira	tiragolumab

Abbreviation	Definition
TNF-α	tumor necrosis factor–α
TPS	tumor proportion score
ULN	upper limit of normal
V20	percentage of lung volume that receives radiation doses of 20 Gy or more
VATS	video-assisted thoracic surgery
VCA	viral capsid antigen
VO_2max	maximal oxygen consumption
VQ scan	ventilation/perfusion scan
[redacted]	

1. BACKGROUND

1.1 BACKGROUND ON NON–SMALL CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide. In the United States, it is the most common cancer in both men and women and accounts for 12%–14% of all new cancer cases. In 2020, there will be an estimated 228,820 new cases of lung cancer, resulting in 135,720 deaths in the United States (Siegel et al. 2020).

Non–small cell lung cancer (NSCLC) 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, sarcomatoid carcinoma, and are of poorly differentiated histology.

The overall 5-year survival rate for advanced disease (Stage IVA and IVB) is 0%–10%, (Goldstraw et al. 2016). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than one-half of patients with NSCLC are diagnosed with metastatic disease, which directly contributes to poor survival prospects.

1.2 TREATMENT OPTIONS FOR RESECTABLE EARLY-STAGE 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. 2020). 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. Adjuvant platinum-based chemotherapy is now the SOC for fully resected (Stage II to IIIB) NSCLC, and neoadjuvant platinum-based chemotherapy is also a widely accepted option as per the National Comprehensive Cancer Network [NCCN] guidelines (NCCN 2020). 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, nab-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).

1.2.1 Adjuvant Treatment for Surgically Resected Early-Stage NSCLC

Adjuvant Systemic Treatment

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 4). The Lung Adjuvant Cisplatin Evaluation (LACE) reported on the results of a pooled analysis of data from five large Phase III trials comparing cisplatin-based adjuvant chemotherapy with no chemotherapy in patients 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 patients 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, 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 patients who had tumors ≥ 4 cm in diameter (HR = 0.69; 95% CI: 0.48 to 0.99).

The Phase III adjuvant E1505 study and the JIPANG study suggest that platinum-based chemotherapy continues to be the current SOC in an unselected early-stage 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.

Recently however, for a select patient population with early-stage resectable NSCLC, targeting a specific oncogenic driver, it was shown that improvements upon the marginal benefit of platinum-based chemotherapy can be achieved in the adjuvant setting. The ADAURA trial demonstrated that patients whose NSCLC had an epidermal growth factor receptor *(EGFR)* mutation achieved significant improvements in median DFS (HR = 0.21;

$p < 0.0001$) with the addition of adjuvant osimertinib with or without platinum-based chemotherapy after surgery (Herbst et al. 2020).

In addition, with the successful development of cancer immunotherapy (CIT) in advanced NSCLC, Phase III adjuvant studies of anti–programmed death-ligand 1 (PD-L1)/anti–programmed death–1 (anti–PD-1) inhibitors (atezolizumab, nivolumab, pembrolizumab, and durvalumab) are currently being conducted in patients with resectable early-stage NSCLC, and perhaps may improve upon the modest survival benefit of platinum-based chemotherapy alone when combined or sequentially administered with platinum-based chemotherapy.

Immune checkpoint inhibitors have transformed the treatment paradigm of solid tumors, including NSCLC, but approvals for NSCLC were previously limited to advanced or metastatic disease settings. Atezolizumab was the first immunotherapy approved for the adjuvant treatment of early-stage resectable PD-L1+ stage II-IIIA NSCLC based on the IMpower010 trial. At the planned interim analysis of the DFS primary endpoint, IMpower010 demonstrated a statistically significant improvement in DFS in the stage II-IIIA PD-L1 $\geq$1% TC analysis population with a hazard ratio (HR) of 0.66 (95% CI: 0.5, 0.88). 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, NE) in the BSC arm (Felip et al. 2021). In the PD-L1 SP263 $\geq$50% TC Stage II-IIIA population the unstratified HR was 0.49 (95% CI: 0.29, 0.81) without EGFR mutations or ALK rearrangements. At a later pre-specified exploratory analysis of OS suggested a trend in favor of atezolizumab over BSC in the PD-L1 SP263 $\geq$1% TC Stage II-IIIA population (stratified HR=0.77; 95% CI: 0.51, 1.17) and a clinically meaningful improvement in the PD-L1 SP263 $\geq$50% TC Stage II-IIIA population without EGFR mutations or ALK rearrangements (unstratified HR = 0.42; 95% CI: 0.23, 0.78) was reported (Felip et al. 2021).

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.

1.2.2 Neoadjuvant Treatment for Surgically Resectable NSCLC Population

Neoadjuvant chemotherapy is another approach to the treatment of resectable early-stage 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 patients who received neoadjuvant treatment versus surgery alone (HR = 0.69; 95% CI: 0.58 to 0.82).

It is important to note that many Phase III neoadjuvant studies were closed early because of positive outcomes in Phase III adjuvant trials. Nevertheless, as a result of these reports, neoadjuvant platinum-based chemotherapy is considered another SOC option for patients with resectable early-stage NSCLC.

1.3 BACKGROUND ON NEOADJUVANT TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS FOR RESECTABLE NSCLC

In the Phase II AAAQ3153 study, 30 patients with resectable early-stage NSCLC received four cycles of neoadjuvant atezolizumab concurrently with carboplatin and nab-paclitaxel. Seventy-seven percent of these patients had Stage IIIA disease. The results were encouraging, with 17 patients (57%) experiencing a major pathological response (MPR) and 10 patients (33%) experiencing a pathological complete response (pCR) and supported further study of combining atezolizumab with chemotherapy as neoadjuvant treatment (Shu et al. 2020).

In the Phase II Study ML39236 (LCMC3) patients with resectable early-stage NSCLC received two cycles of single agent neoadjuvant atezolizumab. The results were encouraging with 30 patients (21%) of the primary efficacy population (n = 144) experiencing a MPR. Four patients (3%) experienced treatment-related delays of their surgery (surgery performed > 28 days after last dose of neoadjuvant atezolizumab) and 5 patients (3%) experienced intraoperative complications. An R0 resection rate of 92% was observed (Lee et al. 2021).

In the Phase II GECP 16/03 (NADIM) study conducted in Spain, patients with Stage IIIA NSCLC were treated with three cycles of neoadjuvant paclitaxel, carboplatin and nivolumab which was well tolerated, with 41 patients (89%) proceeding to surgery with no delays and all undergoing successful R0 resections. Of these 41 patients, 34 patients (83%) achieved a MPR, with 2*6* patients (*63*%) achieving a pCR (Provencio et al. 2020).

In a U.S. study (NCT02259621), 21 patients received two cycles of single agent neoadjuvant nivolumab without reported treatment-related surgical delays. The median time from the administration of the second dose of nivolumab to surgery was 18 days (range: 11–29 days), and 20 of the 21 eligible patients (95%) underwent R0 tumor resection. A MPR was seen in 9/20 of patients (45%) who underwent resection. One patient with Stage IIIA disease had tracheal invasion discovered during surgery, and a complete tumor resection could not be performed (Forde et al. 2018).

In the Phase II NEOSTAR study, 44 patients were randomized to receive three doses of either single agent nivolumab (N) or the combination of nivolumab and ipilimumab (NI) prior to surgery. Of 37 evaluable patients, 11 patients (30%) achieved a MPR (19% N; and 44% NI) and a pCR was seen in 22% of patients (10% N; and 38% NI). No unacceptable toxicity or increased peri-operative morbidity/mortality were noted (Cascone et al. 2019).

These data provide proof-of-concept evidence that use of single agent checkpoint inhibitors (CPIs) or combination of CPIs, with or without chemotherapy, in the neoadjuvant setting is clinically promising and provides a strong rationale for further investigation.

With the successful development of CIT in advanced NSCLC, several neoadjuvant and *perioperative* studies of anti–PD-L1/PD-1 inhibitors (atezolizumab, nivolumab, pembrolizumab, and durvalumab) are currently being conducted in early stage resectable NSCLC, and perhaps may improve upon the modest survival benefit of platinum-b ased chemotherapy alone when combined with and/or sequentially administered with platinum-based chemotherapy.

In the Phase III CheckMate 816 trial, 385 patients were randomized to receive three cycles of neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. A statistically significant improvement in the primary endpoint of pCR was observed (OR = 13.94 [99% CI: 3.49–55.75]; $p < 0.0001$) with 24% of patients in the nivolumab plus chemotherapy arm achieving pCR compared with 2.2% of patients in the chemotherapy alone arm (Forde et al. 2021). The pCR benefit was consistent across disease stages, histologies, and PD-L1 expression levels. Likewise, significant improvement in MPR was also observed with 36.9% of patients in the nivolumab plus chemotherapy arm achieving MPR versus 8.9% in the chemotherapy alone arm (OR =5.70 [95% CI: 3.16–10.26]). Importantly, nivolumab plus chemotherapy was tolerable, and the addition

of nivolumab to chemotherapy did not increase post-surgical complication (Spicer et al. 2021). Numerically, a greater percentage of patients treated with nivolumab plus chemotherapy had definitive surgery and complete resection, and fewer patients underwent pneumonectomy.

KEYNOTE-671 is a Phase III, randomized, double blinded trial evaluating neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab in resectable Stage IIA to IIIB NSCLC with dual primary endpoints of event-free survival (EFS) and OS. With a median follow-up of 25.2 months, the results demonstrated a median EFS of not yet reached (95% CI: 34.1-not yet reached) in the pembrolizumab arm compared with 17.0 months (95% CI: 14.3-22.0) in the control arm (HR = 0.58 [95% CI: 0.46-0.72], p <0.00001), and a median OS of not yet reached in the pembrolizumab arm (95% CI: not yet reached-not yet reached) compared with 45.5 months (95% CI: 42.0-not yet reached) in the control arm (HR=0.73 [95% CI: 0.54-0.99], p 0.02124). Regarding resectability, 82.1% of patients in the treatment arm and 79.4% of patients in control arm underwent definitive surgery. For the key secondary endpoints, the pCR rate among patients who received pembrolizumab was 18.1% (95% CI: 14.5%22.3%) versus 4% (95% CI: 2.3%6.4%) for those who received chemotherapy alone (overall response [OR], 14.2; 95% CI: 10.118.7, p <0.00001) (Wakelee et al. 2023). The treatment regimen was approved by the FDA.

Another perioperative Phase III trial AEGEAN is a randomized, double blinded trial evaluating neoadjuvant durvalumab plus chemotherapy followed by adjuvant durvalumab in resectable Stage IIA to IIIB NSCLC with dual primary endpoints of pCR and EFS. With a median follow-up of 11.7 months, the results demonstrated a median EFS of not yet reached (95% CI:31.9-not yet reached) in the durvalumab arm compared with 25.9 months (95% CI: 18.9-not yet reached) in the control arm (HR=0.68 [95% CI: 0.53-0.88], p=0.003902). The pCR rate among patients who received durvalumab was 17.2% versus 4.3% for those who received chemotherapy alone (OR, 13.0; 9.5% CI: 8.7-17.6, p <0.000036). Regarding resectability, 80.6% of patients in the treatment arm and 80.7% of patients in the control arm underwent definitive surgery (Heymach et al. 2023). These results show that perioperative durvalumab is a potential new treatment option for stage II to IIIB NSCLC before and after surgery, however, there have not been any Health Authority approvals to date.

China only Phase III Neotorch trial is randomized, double-blinded trial evaluating neoadjuvant toripalumab plus chemotherapy followed by one cycle of adjuvant toripalumab plus chemotherapy and then adjuvant toripalimab monotherapy in resectable stage II-III NSCLC. The primary efficacy endpoints are EFS for stage III, EFS for ITT, major pathological response (MPR) for Stage III, and MPR for ITT. The first interim analysis was only for Stage III patients. With a median follow-up of 18.25 months, the results demonstrated a median EFS of not reached (95% CI: 24.4-not yet reached) in the toripalimab arm compared with 15.1 months (95% CI: 10.621.9) in the control arm (HR=0.40 [95% CI:0.277-0.565], p <0.0001) for Stage III patients.

The MPR rate among patients with Stage III disease who received toripalimab was 48.5% (95% CI: 41.455.6) versus 8.4% (95% CI: 5.013.1) for those who received chemotherapy alone (OR, 40.2 [95% CI: 32.248.1], p <0.0001]. Regarding resectability, 82.2% of patients in the treatment arm and 73.3% of patients in the control arm underwent surgery, with 95.8% and 92.6% of patients with R0 resection, respectively. The addition of toripalimab to perioperative chemotherapy showed statistically significant improvements in EFS for patients with Stage III NSCLC with a manageable safety profile (Lu et al. 2023).

CheckMate-77T is a Phase III, randomized, double blinded trial evaluating neoadjuvant nivolumab plus chemotherapy followed by adjuvant nivolumab in resectable Stage IIA to IIIB NSCLC. The study met its primary endpoint of improved EFS at the first interim analysis assessed by blinded Independent Central Review (Cascone et al. 2023). With a median follow up of 25.4 months, the results demonstrated a median EFS of not yet reached (95% CI: 28.9-not yet reached) in the nivolumab arm compared with 18.4 months (95% CI: 13.6-28.1) in the control arm (HR =0.58 [9.5% CI: 0.43-0.81], p <0.00025). The MPR rate among patients who received nivolumab was 35.4% (95% CI: 29.2-41.9%) versus 12.1% (95% CI: 8.2-17.0) for those who received chemotherapy alone (OR, 4.01 [95% CI: 2.48-6.49). The pCR rate among patients who received nivolumab was 25.5% (95% CI: 19.8-31.5) versus 4.7% (95% CI, 2.4-8.3) for those who received chemotherapy alone (OR, 6.64 [95% CI: 3.40-12.97].

1.4 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody 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.

[redacted]

Atezolizumab is approved 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.

1.5 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody 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 patients with cancer.

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

1.6 BACKGROUND ON BLOCKADE OF THE TIGIT PATHWAY IN CANCER AS A POTENTIAL ANTI-CANCER THERAPY

TIGIT is a novel immune inhibitory receptor that is a member of the Ig super family (Yu et al. 2009; Manieri et al. 2017). 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% to 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. Early nonclinical results using genetically deficient

mice and blocking antibodies reveal a key role for TIGIT in regulating T-cell responses. 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 patients.

1.7 COMBINED INHIBITION OF THE TIGIT AND PD-L1/PD-1 PATHWAYS AS 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 patients with locally advanced or metastatic malignancies. [redacted]

[redacted]

Tiragolumab was further evaluated in patients with PD-L1 selected advanced NSCLC (tumor proportion score [TPS] ≥1%) in the Phase II, global, randomized, double-blind, placebo-controlled CITYSCAPE study. As of the clinical cutoff date of 2 December 2019, the confirmed objective response rate (ORR) in the ITT population was higher in the tiragolumab combined with atezolizumab arm (37%) than in the placebo combined with atezolizumab arm (21%). Investigator-assessed progression-free survival (PFS) was also improved with a stratified HR of 0.58 (95% CI: 0.38 to 0.89), with a median PFS not estimable and 3.9 months in the tiragolumab combined with atezolizumab arm compared to the placebo combined with atezolizumab

[redacted]

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.

1.8 COMBINED INHIBITION OF TIGIT AND PD-L1/PD-1 PATHWAYS IN COMBINATION WITH CHEMOTHERAPY

Several Phase III metastatic studies, including MK-3475-189 (KEYNOTE-189), MK-3475-407 (KEYNOTE-407), GO29436 (IMpower150), and GO29537 (IMpower130), have documented that, when co-administered with chemotherapy, the efficacy benefit of PD-L1/PD-1 inhibitors extends across all PD-L1 expression subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019).

The data are consistent with the known effects of chemotherapy on the tumor microenvironment that may potentiate the effects of immunotherapies. In addition to direct cytotoxicity, which increases release of tumor antigens and enhances immunogenicity, chemotherapy has been shown to increase expression of PD-L1 (Zhang et al. 2008) and increase levels of CD155 (PVR), the ligand for TIGIT (Yoshida et al. 2019). The expectation that tiragolumab will further enhance atezolizumab efficacy in the context of chemotherapy is supported by nonclinical evidence that the TIGIT pathway is associated with immune dysfunction and chemoresistance (Blake et al. 2016; Burugu et al. 2018). In lung cancer models, TIGIT expression on T cells contributed to

carboplatin chemoresistance through the upregulation of CD155 and subsequent T-cell dysfunction (Anestakis et al. 2020).

Furthermore, an exploratory study in gastric cancer has shown that after treatment with platinum chemotherapy, patients with a higher percentage of CD8+TIGIT+ T cells had increased rates of cancer relapse and shorter DFS (Tang et al. 2019). Because the TIGIT pathway is associated with immune dysfunction and chemoresistance, these findings suggest that TIGIT blockade to restore T-cell function could potentially improve outcomes for patients undergoing chemotherapy. In support of this hypothesis, in vitro studies have shown that TIGIT blockade countered the suppression of T-cell proliferation and activation following chemotherapy (Tang et al. 2019).

Collectively, the data and preliminary results of Study GO30103 and CITYSCAPE have led to the hypothesis that anti–TIGIT treatment (tiragolumab) in combination with anti–PD-L1 treatment (atezolizumab) plus chemotherapy may result in enhanced and more durable responses. This combination is currently under evaluation in other indications.

1.9 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.9.1 Study Rationale

TIGIT is an inhibitory immunoreceptor that can limit the effector function of tumor-associated lymphocytes. Unlike other inhibitory co-receptors, TIGIT is often coordinately expressed with PD-1 on tumor-infiltrating T cells in multiple tumors, including NSCLC. In the Phase Ib portion of Study GO30103, evaluating tiragolumab in combination with atezolizumab PRs occurred in patients with metastatic cancers, including NSCLC, with varying degrees of PD-L1 and/or TIGIT expression (Bendell et al. 2020). The combination of atezolizumab with tiragolumab was tolerated in the Phase Ib portion of the study, with a safety profile consistent with prior observations of atezolizumab.

Consistent with the Phase Ib portion of Study GO30103, the combination of atezolizumab with tiragolumab was tolerated in the Phase II 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 infusion-related reactions (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 light of the evidence of clinical activity of atezolizumab plus tiragolumab in NSCLC and the need to improve survival and decrease recurrence rates for patients with resectable early-stage NSCLC, the Sponsor is conducting this Phase II study GO42501. The study is designed to evaluate whether neoadjuvant therapy with the combination of atezolizumab and tiragolumab, with or without platinum-based chemotherapy, is safe and tolerable and does not have a deleterious effect on surgical outcomes in patients with resectable Stage II, IIIA, and select IIIB (T3N2) NSCLC. This study is also designed to evaluate potential anti-tumor effects of neoadjuvant atezolizumab plus tiragolumab alone (Cohort A) or with platinum-based chemotherapy (Cohort B), as measured by MPR.

Given that the additional atezolizumab plus tiragolumab benefit relative to atezolizumab alone was primarily observed in patients with high PD-L1 expression in CITYSCAPE, Cohort A will include only patients with tumors having high PD-L1 expression [redacted] Patients in Cohort A (hereafter referred to as Cohort A [PD-L1 high]) will receive atezolizumab plus tiragolumab as neoadjuvant treatment. After surgery, patients will receive adjuvant treatment with either additional cycles of atezolizumab plus tiragolumab or platinum-based chemotherapy (physician's choice of protocol-defined regimen) to ensure all patients have the opportunity for SOC treatment with chemotherapy.

The clinical benefit of chemotherapy combined with PD-L1/PD-1 inhibitors has been documented by improved OS and PFS in metastatic NSCLC patients throughout all PD-L1 subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019) and is being further studied in ongoing early-stage NSCLC studies. The expectation that tiragolumab will enhance

atezolizumab efficacy in the context of chemotherapy in NSCLC is supported by preclinical evidence that the TIGIT pathway is associated with immune dysfunction and chemoresistance. Thus, TIGIT blockade may restore T-cell function and improve outcomes in patients treated with chemotherapy (see Section 1.8). This evidence, as well as data from CITYSCAPE, support the hypothesis that tiragolumab in combination with atezolizumab and chemotherapy may result in enhanced and more durable responses across PD-L1 subgroups. To further study this hypothesis, patients in Cohort B will include patients across all PD-L1 subgroups who will receive atezolizumab plus tiragolumab plus platinum-based chemotherapy (physician's choice of protocol-defined regimen) as neoadjuvant treatment. After surgery, patients in Cohort B (hereafter referred to as Cohort B [PD-L1 all comers]) will receive additional cycles of atezolizumab plus tiragolumab.

Because the safety of the combination of atezolizumab plus tiragolumab in the neoadjuvant setting has yet to be determined, the study will enroll in a stepwise fashion with limited patients for initial evaluation at a limited number of clinical sites (see Section 4.2.1), and the Medical Monitor and a Joint Monitoring Committee (JMC; see Section 3.1.2) will closely monitor surgical outcomes and preliminary efficacy data.

1.9.2 Benefit–Risk Assessment

Data from CITYSCAPE indicate that combination therapy of atezolizumab plus tiragolumab may confer increased efficacy benefit in NSCLC relative to atezolizumab monotherapy in PD-L1 high patients. To date, there is evidence of improved radiographic and pathological responses when combining CPI with chemotherapy in the neoadjuvant setting compared with chemotherapy alone (Provencio et al. 2020; Shu et al. 2020). In addition, there are ongoing safety and efficacy clinical trials of atezolizumab plus tiragolumab, with and without platinum-based chemotherapy, as well as clinical trials of neoadjuvant and adjuvant CPI treatment, with and without platinum-based chemotherapy in NSCLC.

Based on these observations, neoadjuvant therapy with atezolizumab plus tiragolumab, with or without chemotherapy, may improve efficacy outcomes in patients with resectable early-stage NSCLC relative to neoadjuvant chemotherapy alone.
The combination of atezolizumab plus tiragolumab was tolerated in both Study GO30103 and CITYSCAPE. The toxicities of atezolizumab alone and the combination of atezolizumab plus tiragolumab are expected to be similar. Immune-mediated adverse events, although reported at a higher frequency for the atezolizumab plus tiragolumab arm in CITYSCAPE, are generally mild, transient, monitorable, and manageable in nature. The toxicities of the combination of atezolizumab and tiragolumab plus chemotherapy are also expected to be similar to the combination of atezolizumab plus chemotherapy.

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 patients in this trial. Oversight of this study will be provided by the Sponsor's Medical Monitor (see Section 5.4.1). Additionally, a JMC, [redacted], will be formed to evaluate safety data during the study.

Currently available clinical data also indicate that the therapeutic value of tiragolumab is in combination with atezolizumab. Patients who received atezolizumab and tiragolumab as participants in the Phase Ib portion of Study GO30103 (solid tumors, including metastatic NSCLC) and in CITYSCAPE (in metastatic NSCLC) achieved encouraging efficacy outcomes (detailed in Section 1.7).

Given that the addition of tiragolumab to atezolizumab improved efficacy outcomes in metastatic NSCLC in CITYSCAPE (see Section 1.7), it is anticipated that this combined regimen may potentially also improve efficacy in resectable *early stage* 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 (Studies GO41717, GO41767, GO41854, and BO42592).

Given the unmet need that still exists in resectable *early stage* NSCLC, the strength of the scientific hypothesis and the compelling clinical data supporting this study as well as the rigorous safety monitoring proposed, Study GO42501 will provide an initial evaluation of the benefit–risk profile of neoadjuvant atezolizumab plus tiragolumab with or without platinum-based chemotherapy.

This trial will enroll patients with previously untreated resectable Stage II, IIIA, or select IIIB NSCLC. Given the relatively poor prognosis, limited treatment options and more than a decade of little to no improvement in the treatment landscape for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit–risk ratio for atezolizumab in combination with tiragolumab, with or without platinum-based chemotherapy, is expected to be acceptable in this setting.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with lung 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 CPI treatment 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; Wykes and Lewin 2018; Schorer et al. 2020). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

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-γ (IFN-γ) (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab and/or tiragolumab. At this time, there is insufficient evidence for causal association between atezolizumab or tiragolumab 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 CPIs and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab and tiragolumab in combination with chemotherapy.

There are limited data concerning the possible interactions between cancer immunotherapy 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 for Cancer [SITC] 2020).

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

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab and tiragolumab 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 patient 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.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the surgical safety and feasibility of atezolizumab plus tiragolumab alone (Atezo + Tira) or in combination with platinum-based chemotherapy (Atezo + Tira + Chemo) as neoadjuvant treatment for patients with previously untreated locally advanced NSCLC. The study will also evaluate the efficacy, pharmacokinetics, immunogenicity, and safety of neoadjuvant Atezo + Tira or Atezo + Tira + Chemo, followed by adjuvant Atezo + Tira or adjuvant platinum-based chemotherapy (Chemo) as indicated below and detailed in Section 3.1.1.

Table 1 Study treatments administered

Cohort	Neoadjuvant Treatment	Adjuvant Treatment
A (PD-L1 high)	Atezo + Tira	Atezo + Tira
		Chemo [a]
B (PD-L1 all comers)	Atezo + Tira + Chemo	Atezo + Tira

Atezo = atezolizumab; Chemo = platinum-based chemotherapy; PD-L1 = programmed death–ligand 1; Tira = tiragolumab.

[a] Investigator's choice to administer chemotherapy as adjuvant treatment.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., Atezo + Tira, Atezo + Tira + Chemo or chemotherapy).

Specific objectives and corresponding endpoints for the study are outlined in Table 2.

Table 2 Objectives and Corresponding Endpoints

Primary Safety Objectives	Corresponding Endpoints
• To evaluate the safety of Atezo + Tira as neoadjuvant treatment followed by either Atezo + Tira or Chemo as adjuvant treatment • To evaluate the safety of Atezo + Tira + Chemo as neoadjuvant treatment followed by Atezo + Tira as adjuvant treatment	• Incidence and length of surgical delays, incidence of operative and post-operative complications, and/or number of surgical cancellations related to study treatment • Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 [redacted]
Primary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of Atezo + Tira or Atezo + Tira + Chemo as neoadjuvant treatment	• MPR rate, defined as the proportion of patients who achieve MPR, with MPR, defined as ≤ 10% residual viable tumor at the time of surgical resection in the primary tumor, as assessed by the *local* pathology laboratory
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of Atezo + Tira or Atezo + Tira + Chemo as neoadjuvant treatment	• pCR, defined as the absence of any viable tumor cells in both the primary tumor and all sampled lymph nodes at the time of surgical resection, as assessed by the *local* pathology laboratory
• To evaluate the efficacy of Atezo + Tira as neoadjuvant treatment followed by either Atezo + Tira or Chemo as adjuvant treatment • To evaluate the efficacy of Atezo + Tira + Chemo as neoadjuvant treatment followed by Atezo + Tira as adjuvant treatment	• EFS, defined as the time from first dose of study drug to any of the following events, whichever occurs first: disease progression that precludes surgical resection, as assessed by the investigator, or local or distant disease recurrence after surgery, including the occurrence of a new primary NSCLC, or death from any cause

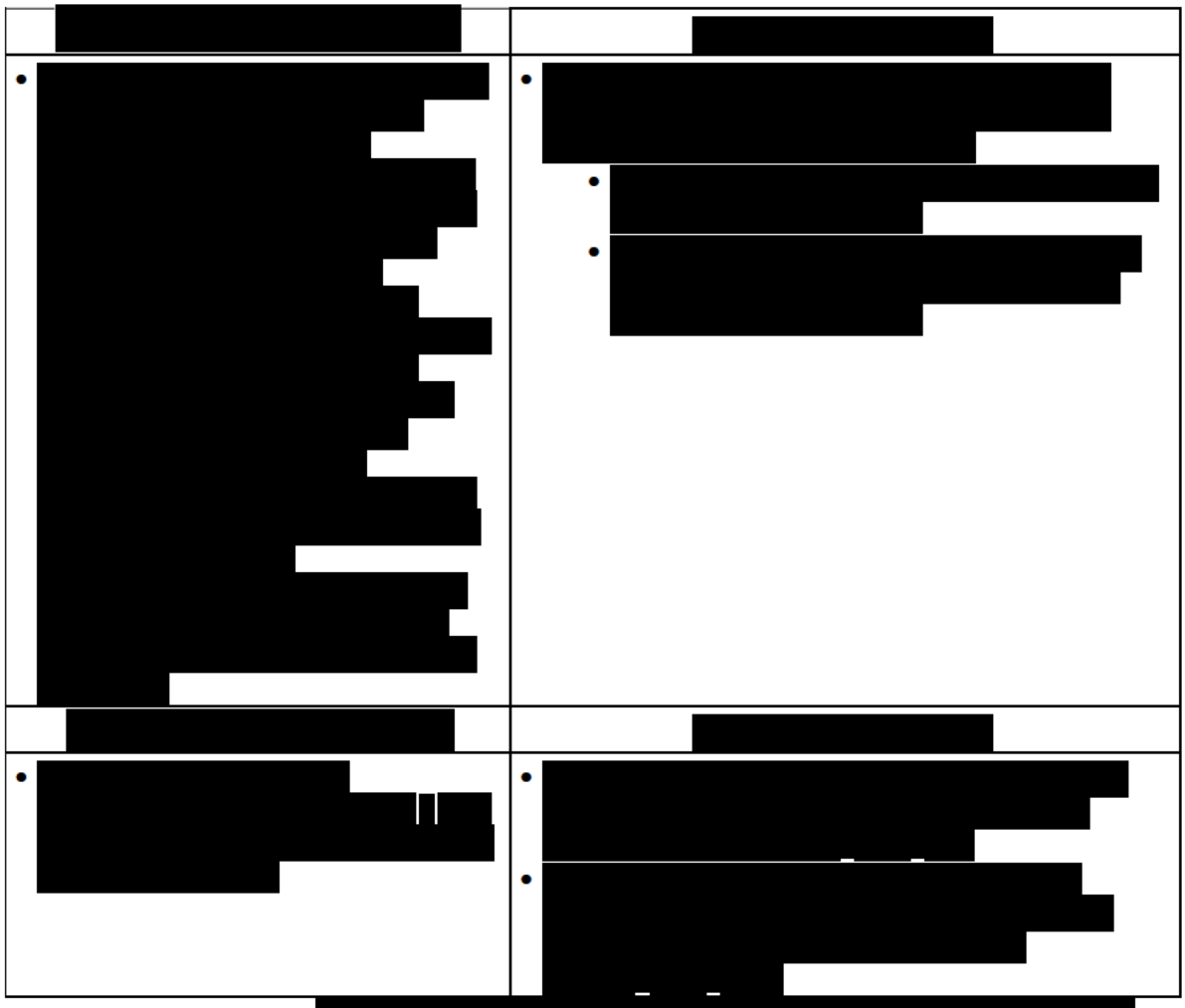
ADA = anti-drug antibody; [redacted]
Atezo + Tira = atezolizumab plus tiragolumab; Atezo + Tira + Chemo = atezolizumab plus tiragolumab plus platinum-based chemotherapy; CRS = cytokine-release syndrome; ctDNA = circulating tumor DNA; EFS = event-free survival; [redacted]
MPR = major pathological response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NSCLC = non–small cell lung cancer; PBMC = peripheral blood mononuclear cell; pCR = pathological complete response; PK = pharmacokinetic; [redacted]

Table 2 Objectives and Corresponding Endpoints (cont.)

[redacted]	[redacted]
• [redacted]	• [redacted] • [redacted]
[redacted]	[redacted]
• [redacted]	• [redacted]
Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the PK profile of atezolizumab and tiragolumab when given in combination	• Serum concentrations of atezolizumab and tiragolumab at specified timepoints
Immunogenicity Objective	Corresponding Endpoints
• To evaluate the immune response to atezolizumab and tiragolumab	• Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
[redacted]	[redacted]
• [redacted]	• [redacted]

ADA=anti-drug antibody; [redacted]
Atezo+Tira=atezolizumab plus tiragolumab; Atezo+Tira+Chemo=atezolizumab plus tiragolumab plus platinum-based chemotherapy; CRS=cytokine-release syndrome; ctDNA=circulating tumor DNA; EFS=event-free survival; [redacted]
MPR= major pathological response; NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NSCLC=non-small cell lung cancer; PBMCs=peripheral blood mononuclear cell; pCR=pathological complete response; PK=pharmacokinetic; [redacted]

Table 2 Objectives and Corresponding Endpoints (cont.)



ADA = anti-drug antibody; Atezo + Tira = atezolizumab plus tiragolumab; Atezo + Tira + Chemo = atezolizumab plus tiragolumab plus platinum-based chemotherapy; CRS = cytokine-release syndrome; ctDNA = circulating tumor DNA; EFS = event-free survival; MPR = major pathological response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NSCLC = non–small cell lung cancer; PBMC = peripheral blood mononuclear cell; pCR = pathological complete response; PK = pharmacokinetic;

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a global Phase II, open-label, multicenter study evaluating the safety and efficacy of neoadjuvant and adjuvant atezolizumab plus tiragolumab, with or without platinum-based chemotherapy, in patients with previously untreated, histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC.

This study is designed to establish proof-of-concept clinical data that neoadjuvant treatment with Atezo + Tira or Atezo + Tira + Chemo is safe, tolerable and does not have a clinically significant negative effect on surgical outcomes in patients with early-stage resectable NSCLC. This study is also designed to evaluate potential anti-tumor effects of neoadjuvant Atezo + Tira or Atezo + Tira + Chemo, as measured by MPR. The study is designed with the flexibility to open new cohorts as new treatment combinations become available.

This study will involve the use of an investigational diagnostic device. PD-L1 status of the NSCLC tumor specimens will be evaluated by a College of American pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory using the commercially available [redacted]

Patients will be assigned to a cohort on the basis of PD-L1 status as outlined in Section 4.2.1 and will receive treatment as follows:

- **Cohort A (PD-L1 high)**: neoadjuvant Atezo + Tira for 4 cycles, followed by surgical resection and either adjuvant Atezo + Tira for 16 cycles or adjuvant chemotherapy for 4 cycles
- **Cohort B (PD-L1 all comers)**: neoadjuvant Atezo + Tira + Chemo for 4 cycles, followed by surgical resection and adjuvant Atezo + Tira for 16 cycles

Selection of the platinum-based chemotherapy regimen will be at the discretion of the investigator, based on histology subtypes and documented at the time of initiation. The following platinum-based chemotherapy options are permitted for this study.

- For non-squamous NSCLC:
  - Cisplatin + pemetrexed
  - Carboplatin + pemetrexed
  - Carboplatin + paclitaxel
- For squamous NSCLC:
  - Carboplatin + gemcitabine
  - Carboplatin + paclitaxel

Surgical specimens will be assessed for pathological response (MPR and pCR) by the investigator's site pathology laboratory. In addition, [redacted]

[redacted]

All patients will complete scheduled tumor assessments of the chest and abdomen by both computed tomography (CT) and positron emission tomography (PET) at screening and by CT only after Cycles 2 and 4 of neoadjuvant treatment. Tumor assessments will continue after surgery until recurrence (see Section 4.5.6). If a disease follow-up assessment shows evidence of disease recurrence, it should be confirmed pathologically and/or by unequivocal radiographic evidence from the scan. [redacted]

[redacted] In the absence of disease recurrence, disease follow-up assessments should continue until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see Section 4.5.6 and Appendix 1 for details).

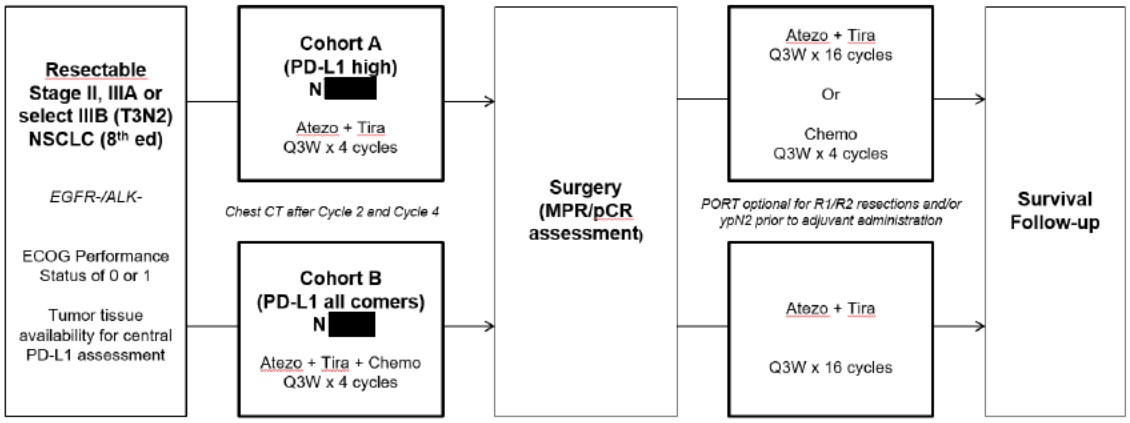
All patients will undergo safety, tolerability, and [redacted] assessments on Day 1 of each cycle in the neoadjuvant treatment phase (both cohorts) and in the adjuvant treatment phase. After treatment discontinuation, patient follow-up will be periodically performed for survival status and any additional anti-cancer treatment.

Safety assessments will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, and laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Adverse events will be graded by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

[redacted] In addition, patients will be provided an opportunity to consent to [redacted] (optional consent required, see Section 4.5.11).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



ALK=anaplastic lymphoma kinase; Atezo=atezolizumab; Chemo=platinum-based doublet chemotherapy; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; *EGFR*=epidermal growth factor receptor; MPR=major pathological response; NSCLC=non–small cell lung cancer; pCR=pathological complete response; PORT=post-operative radiotherapy; Q3W=every 3 weeks; Tira=tiragolumab.

**Note: Originally planned to enroll [redacted] patients in Cohort A, but this cohort has been closed as of Protocol Version 5.*

3.1.1.1 Treatment Assignment and Safety Lead-In

Patients must be eligible for R0 resection with curative intent at screening and must meet all eligibility criteria specified in Section 4.1. Patients who do not meet the criteria for participation in this study (screen failures) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

Treatment Assignment and Safety Lead-In Based on Tumor PD-L1 Status

After providing informed consent, patients will undergo screening procedures, including central assessment of PD-L1 status by the investigational [redacted] Enrollment will be completed in a step-wise manner as follows (see Figure 2), with approximately [redacted] patients enrolled in each of the cohorts. *Cohort A enrollment was closed in September 2023*:

1. Initially there will be a safety lead-in:
   - [redacted]
   - [redacted]
2. The JMC will evaluate the safety of each cohort, and if deemed to be safe:
   - [redacted]
   - [redacted]
3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Safety Lead-In

[redacted]

[redacted]

3.1.1.2 Surgery and Adjuvant Treatment

Patients will undergo surgical resection of their tumor upon completion of four cycles of neoadjuvant therapy. [redacted]

The pre-surgery visit should occur within [redacted] days after the last dose of neoadjuvant treatment; repeat pulmonary function tests (PFTs) (if clinically indicated), as well as associated assessments (see Appendix 1) should be performed in accordance with local institutional practice. The surgical procedure should be performed within [redacted] days after the pre-surgery visit if judged clinically feasible by both the attending surgeon and medical oncologist. Surgical data should be entered on the corresponding electronic Case Report Form (eCRF) as soon as possible after surgery, especially during the safety lead-in, so that assessment of surgical delays, cancellations, or complications can be completed in a timely manner. See Section 4.3.3 for guidance on the surgical treatment plan.

Patients who are found to have disease progression at scheduled tumor assessments (after Cycle 2 and Cycle 4) or at any time during neoadjuvant treatment and are still deemed resectable and non-metastatic will proceed to surgery if amenable and will remain eligible for all study treatment and evaluations.

Patients who discontinue neoadjuvant treatment early because of disease progression and do not proceed to surgery will be discontinued from additional in-clinic study procedures and will proceed to receive other treatment as determined by the investigator. [redacted]

After surgical resection, patients will continue to receive adjuvant Atezo+Tira or adjuvant chemotherapy (Cohort A [PD-L1 high] only) until one of the following occurs: administration of up to four cycles of adjuvant chemotherapy per local SOC, 16 cycles of adjuvant Atezo+Tira, unacceptable toxicity, disease recurrence, death, or patient and/or physician decision to discontinue study treatment.

3.1.2 Joint Monitoring Committee

A JMC, [redacted], will be formed to evaluate safety data during the study. The external experts share with the Sponsor the responsibility for trial monitoring and are invited to attend all review meetings and participate in all data reviews. [redacted] The JMC will follow a charter that outlines the JMC's roles and responsibilities.

The JMC will review data to assess potential surgical delays, cancellations, or complications related to study treatment during the safety lead-in as described in Section 3.1.1.1. After the safety lead-in, safety data will be reviewed on a periodic basis [redacted]

[redacted]

After reviewing the data, the JMC will provide a recommendation to the Sponsor as described in the JMC Charter. [redacted]

[redacted]

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs, which is expected to occur approximately 3 years after the last patient receives the final dose of study drugs after surgery.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5–6 years.

3.3 DURATION OF PARTICIPATION

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

3.4 RATIONALE FOR STUDY DESIGN

This study will evaluate the surgical safety and feasibility of Atezo + Tira or Atezo + Tira + Chemo as neoadjuvant treatment for patients with previously untreated locally advanced NSCLC. The study will also evaluate the efficacy, pharmacokinetics, immunogenicity, and safety of neoadjuvant Atezo + Tira or Atezo + Tira + Chemo followed by adjuvant Atezo + Tira or adjuvant chemotherapy.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4.2 Rationale for Patient Population

This study will enroll patients with resectable Stage II, IIIA, and select IIIB (T3N2 only) NSCLC as determined at screening. [redacted] will be enrolled in Cohort A (PD-L1 high), while all comers (regardless of PD-L1 expression level) will be enrolled in Cohort B (PD-L1 all comers).

Neoadjuvant and adjuvant chemotherapy has shown significant but modest benefit for patients with early-stage resectable NSCLC, but there is still a substantial unmet need for improvement in outcomes in this treatment setting.

Tumor-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens. Boosting tumor-specific T-cell immunity in this setting by blocking the PD-L1 and TIGIT pathways may result in deeper and more durable responses than those observed with standard chemotherapy alone (Merritt et al. 2003;

Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

Given the strong data from CITYSCAPE showing the magnitude of benefit in the PD-L1 TPS $\geq$ 50% population, and the need to improve survival and decrease recurrence rates for patients with resectable early-stage NSCLC, this study will examine the efficacy of Atezo + Tira combination as a *chemotherapy-free* option. A chemotherapy-free option for patients with resectable NSCLC would be a landmark improvement for patients and may spare patients the early and late toxicity associated with chemotherapy.

3.4.3 Rationale for Major Pathological Response as Primary Endpoint

The primary efficacy objective of this study is to evaluate the efficacy of neoadjuvant treatment with Atezo + Tira or Atezo + Tira + Chemo in patients with resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC as measured by *local* pathology *laboratory assessed*-MPR.

While OS is the standard in evaluating clinical benefit in adjuvant and neoadjuvant NSCLC trials, readout of OS often takes many years, especially in early-stage disease. Thus, adopting meaningful surrogate endpoints may expedite the evaluation of new therapies and bring new treatments to NSCLC patients sooner. Pathological response after surgical resection of NSCLC has been proposed as a surrogate endpoint for OS (Hellmann et al. 2014). Hellmann et al. (2014) cited the U.S. Food and Drug Administration's (FDA's) definition of the surrogate endpoint in which the endpoint should be "reasonably likely to predict clinical benefit". They advocate that using pathological response in the neoadjuvant setting meets this definition based on three findings: 1) pathological response strongly correlates to OS; 2) pathological response is reflective of neoadjuvant chemotherapy; and 3) the degree of pathological response correlates with the degree of OS benefit.

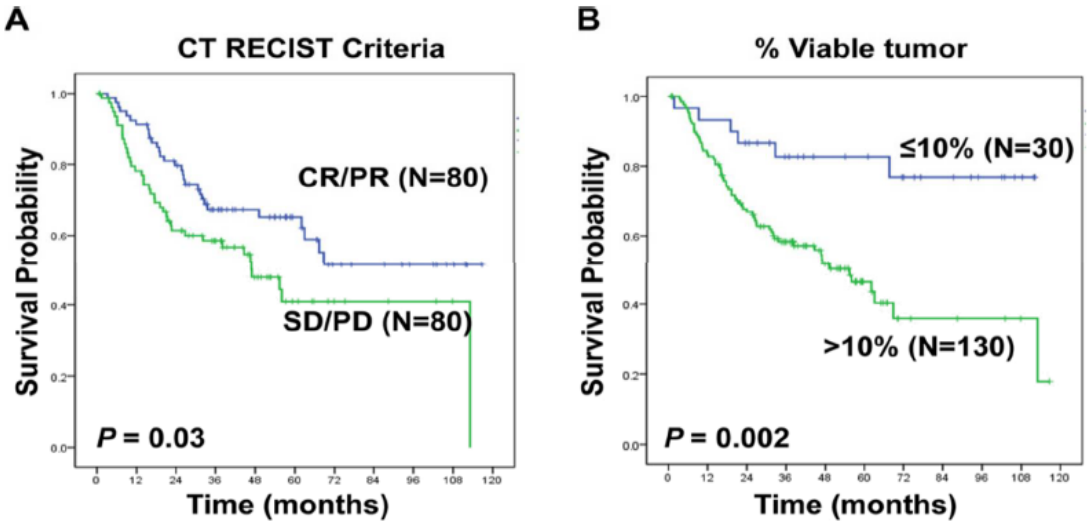
Use of pathological response as a surrogate endpoint is not without precedent. Trials for breast cancer have used pCR to evaluate the efficacy of neoadjuvant treatment. However, pCR rates have varied in neoadjuvant NSCLC studies. Furthermore, relatively low pCR rates reported in NSCLC may not translate into a clinically significant OS benefit, hence restricting the utility of pCR as a surrogate survival endpoint in NSCLC trials. In fact, few trials have reported corollary survival data for pCR in NSCLC because of low pCR rates (median rate 4%) (Hellmann et al. 2014).

Instead of pCR, Hellman et al. (2014) proposed the use of MPR, defined as $\leq$ 10% residual viable tumor tissue, as a survival surrogate for patients with resectable NSCLC receiving neoadjuvant chemotherapy treatment. This is based on studies in which investigators, in acknowledgment of the rarity of pCR in NSCLC, considered other definitions of pathological response, including residual viable tumor as a surrogate survival endpoint. Junker et al. (1997) performed pathological analysis of 40 tumors

from patients with Stage IIIA and IIIB disease who were given sequential neoadjuvant chemotherapy treatment, chemoradiotherapy, and surgical resection. Patients with ≤10% residual tumor in this group had a median survival of 36 months, while patients who had >10% residual viable tumor tissue had a median survival of 14 months.

Two prospective trials reported an MPR rate of approximately 22% with neoadjuvant chemotherapy in NSCLC. The first study noted that of the 90 patients with Stage IIIA disease who received neoadjuvant chemotherapy (cisplatin+docetaxel), the median pathological response (amount of tumor necrosis and fibrosis) was 60%, with a median OS of 61 months compared with 22 months in patients with ≤60% pathological response (Betticher et al. 2006). Another study showed that of the 50 patients who received neoadjuvant chemotherapy (cisplatin+docetaxel) in combination with bevacizumab, patients with MPR had a significantly longer 3-year survival rate compared with patients who did not achieve MPR (61 months vs. 22 months, respectively) (Chaft et al. 2013). A retrospective study from the MD Anderson Cancer Center by William and colleagues (William et al. 2013) showed that in 160 patients who received neoadjuvant platinum-based chemotherapy, MPR was a stronger predictor of OS than clinical Response Evaluation Criteria in Solid Tumors (RECIST) response (see Figure 3).

Figure 3 Overall Survival by Clinical Response and by Pathological Response



CR/PR = complete response/partial response; CT RECIST = computed tomography Response Evaluation Criteria in Solid Tumors; SD/PD = stable disease/progressive disease.
Source: William et al. 2013.

The Sponsor believes that there is a significant rationale for the use of MPR as a surrogate endpoint based on its correlation to the magnitude of improvement in OS. Currently, there are ongoing global Phase III neoadjuvant registrational trials of chemotherapy plus PD-L1/PD-1 inhibitors vs. chemotherapy alone assessing MPR as a primary or secondary objective. Use of MPR as a surrogate endpoint has the potential to increase the effectiveness of clinical studies and to accelerate new therapies for

patients with NSCLC. The Phase II NADIM and AAAQ3153 trials provided preliminary evidence of a correlation between MPR and PFS, further supporting the relevance of MPR as a potential survival surrogate endpoint in early stage resectable NSCLC (Provencio et al. 2020; Shu et al. 2020).

[redacted]

[redacted]

3.4.5 Rationale for Patient-Reported Outcome Assessments

The long-term goals of lung cancer surgery include improved length and quality of life (Win et al. 2005). Although lung resection remains the most effective treatment for patients with resectable NSCLC, these patients are at increased risk of complications from surgery and of functional impairment post-operatively (Win et al. 2005).

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting

adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects.

Previous studies have shown that patients with resectable lung cancer present with mild to moderate symptoms of fatigue, dyspnea, and cough and that patients' health-related quality of life (HRQoL) scores tend to return to preoperative levels 6–9 months after surgery. To comprehensively capture disease and treatment burden from the patients' perspective, patient-relevant endpoints of symptom severity and their impact on function and HRQoL will be collected using validated patient-reported measures. [redacted]

In order to evaluate the tolerability of neoadjuvant and adjuvant Atezo+Tira, patients will be asked to report on their experience related to study treatment-related symptoms by [redacted] (see Appendix 8). These symptoms were identified as being salient to patients' experience with Atezo+Tira on the basis of the combined safety profile. Data generated from these instruments will inform patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the benefit-risk profile of Atezo+Tira.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately [redacted] patients with Stage II, IIIA, or select IIIB (T3N2 only) will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the inclusion criteria listed below to be eligible for study entry.

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically or cytologically confirmed Stage II, IIIA, or select IIIB (T3N2 only) NSCLC of squamous or non-squamous histology

[redacted]

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

[redacted]

- Solid or subsolid appearance of NSCLC on CT scan with no appearance of purely ground-glass opacity (GGO)

  For subsolid lesions, the tumor size (i.e., clinical T stage) should be measured based on solid component only, exclusive of the GGO component.

- Eligible for R0 resection with curative intent at the time of screening, as confirmed by the operating attending surgeon and involved medical oncologist prior to study enrollment (see Section 4.3.3)
- Adequate pulmonary function to be eligible for surgical resection with curative intent, as assessed by PFTs performed within 6 months of planned resection and repeated at screening, if clinically indicated, including lung volumes, spirometry, and a diffusion capacity; and meeting at least one of the following criteria:
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]

- Eligible to receive a platinum-based chemotherapy regimen
- Measurable disease, as assessed by the investigator per RECIST v1.1 (see Appendix 3)
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Normal life expectancy, excluding lung cancer mortality risk
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

- Negative HIV test at screening
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, and 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin or cisplatin. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 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). 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  Women who would like to become pregnant after study treatment discontinuation should seek advice on oocyte cryopreservation prior to initiation

of study treatment because of the possibility of irreversible infertility due to treatment with cisplatin and carboplatin.

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

  With a female partner of childbearing potential, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period, for 90 days after the final dose of tiragolumab, and for 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin or cisplatin. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period for 90 days after the final dose of tiragolumab, and for 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin or cisplatin to avoid exposing the embryo.

  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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  Men who would like to father a child after study treatment initiation should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from chemotherapies used in this study.

4.1.2 Exclusion Criteria

Patients who meet any of the criteria listed below will be excluded from study entry.

- NSCLC with histology of large cell neuroendocrine carcinoma, sarcomatoid carcinoma, or NSCLC not otherwise specified
- Small cell lung cancer (SCLC) histology or NSCLC with any component of SCLC
- Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures
- Any prior therapy for lung cancer, including immunotherapy, chemotherapy, or radiotherapy

- Active or history of autoimmune disease or immune deficiency, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- 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
- NSCLC with an activating *EGFR* mutation or *ALK* fusion oncogene

[redacted]

ALK and/or *EGFR* status may be assessed locally or submitted for central laboratory testing.

  - [redacted]
  - [redacted]

- Known c-ros oncogene 1 (*ROS1*) rearrangement

  [redacted]

- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of 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, non-melanoma 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, in the opinion of the investigator, could impact patient 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 patient 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, within 90 days after the final dose of tiragolumab, or within 5 months after the final dose of atezolizumab

  [redacted]

- [redacted]
- [redacted]

  [redacted]

- [redacted]
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, anti–TIGIT, and anti–PD-L1 therapeutic antibodies.
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [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
- Known allergy or hypersensitivity to any component of the chemotherapy regimen the patient may receive during the study
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment, within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of pemetrexed, gemcitabine, paclitaxel, carboplatin, or cisplatin

[redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

This is an open-label study. After written informed consent has been obtained, a patient will be assigned a screening number from the interactive voice or web-based response system (IxRS). Upon completion of all screening procedures and assessments have been completed, the Surgical Feasibility Form has been reviewed and confirmed by the Sponsor, and eligibility has been established for a patient, the study site will obtain the

patient's identification number (distinct from the screening number) and treatment assignment from the IxRS.

[redacted] at the [redacted]) will be enrolled in Cohort A (PD-L1 high) while all comers (regardless of PD-L1 expression level) will be enrolled in the Cohort B (PD-L1 all comers) (see Section 3.4.2). Enrollment will be completed in a step-wise manner as follows (see Figure 2), with approximately [redacted] patients enrolled in each of the cohorts:

1. Initially there will be a safety lead-in:
   - [redacted]
   - [redacted]
2. The JMC will evaluate the safety of each cohort, and if deemed to be safe:
   - [redacted]
   - [redacted]
3. [redacted]

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and tiragolumab. Gemcitabine, paclitaxel, pemetrexed, carboplatin, and cisplatin are considered non-investigational medicinal products.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab

Atezolizumab will be supplied by the Sponsor as a sterile liquid in a single-use, 20 mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.1.2 Tiragolumab

Tiragolumab will be supplied by the Sponsor as a sterile liquid in a single-use, 15 mL glass vial. The vial contains approximately 10 mL (600 mg) of tiragolumab.

For further information on the tiragolumab formulation, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

4.3.1.3 Carboplatin, Cisplatin, Pemetrexed, Gemcitabine, and Paclitaxel

Carboplatin, cisplatin, pemetrexed, gemcitabine, and paclitaxel will be used in the commercially available formulation where allowed by local regulations.

For more information on the formulation and packaging of carboplatin, cisplatin, pemetrexed, gemcitabine, and paclitaxel, please refer to the local prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Each study treatment component will be administered at the doses and frequency specified in Table 3.

Table 3 Study Treatment Component Regimens

Study Treatment Component	Timing
Neoadjuvant Treatment Phase	
Cohort A (PD-L1 high)	
Atezolizumab (1200 mg IV) Tiragolumab (600 mg IV)	Day 1 of each 21-day cycle for 4 cycles Day 1 of each 21-day cycle for 4 cycles
Cohort B (PD-L1 all comers)	
Atezolizumab (1200 mg IV) Tiragolumab (600 mg IV)	Day 1 of each 21-day cycle for 4 cycles Day 1 of each 21-day cycle for 4 cycles
Carboplatin (IV, initial target AUC of 5 or 6 mg/mL/min) [a]	Day 1 of each 21-day cycle for 4 cycles
Cisplatin (75 mg/m^2 IV)	Day 1 of each 21-day cycle for 4 cycles
Pemetrexed (500 mg/m^2 IV)	Day 1 of each 21-day cycle for 4 cycles
Gemcitabine (1000 or 1250 mg/m^2 IV) [b]	Days 1 and 8 of each 21-day cycle for 4 cycles
Paclitaxel (175 or 200 mg/m^2 IV) [c]	Day 1 of each 21-day cycle for 4 cycles
Adjuvant Treatment Phase	
Cohort A (PD-L1 high)	
Atezolizumab (1200 mg IV) Tiragolumab (600 mg IV) or Platinum-based chemotherapy (see Neoadjuvant Treatment Phase, Cohort B for chemotherapy dosing information)	Day 1 of each 21-day cycle for 16 cycles Day 1 of each 21-day cycle for 16 cycles See Neoadjuvant Treatment Phase, Cohort B for chemotherapy dosing information
Cohort B (PD-L1 all comers)	
Atezolizumab (1200 mg IV) Tiragolumab (600 mg IV)	Day 1 of each 21-day cycle for 16 cycles Day 1 of each 21-day cycle for 16 cycles

AUC = area under the concentration–time curve; IV = intravenous.

[a] Carboplatin should be administered at initial target of AUC 5 mg/mL/min when given after pemetrexed or gemcitabine, and administered at initial target of AUC 6 mg/mL/min when given after paclitaxel.

[b] Gemcitabine should be administered at 1000 mg/m^2 for each dose when given before carboplatin.

[c] [redacted].

The neoadjuvant treatment phase will consist of four cycles of Atezo + Tira or Atezo + Tira + Chemo. Each cycle will be 21 days in duration. On Day 1 of each cycle, all eligible patients will be administered study drug infusions in the following order:

- **Cohort A (PD-L1 high):** [redacted]
- **Cohort B (PD-L1 all comers):** Investigator will administer one of the listed regimens based on histology subtype and local SOC.
  - [redacted]
  - [redacted]
  - [redacted]

Atezolizumab (1200 mg) and tiragolumab (600 mg) will be administered at a fixed dose.

[redacted]

For Cycle 1, premedication for primary prophylaxis (antihistamines, antipyretic *medication*s, and/or analgesics) of atezolizumab and tiragolumab is not permitted. Patients should receive anti-emetics and IV hydration for the selected chemotherapy backbone regimen according to the local SOC and manufacturer's instruction. However, because of the immunomodulatory effects of corticosteroids, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2.1). A list of premedication for pemetrexed is provided in Table 4. All medications must be recorded on the appropriate Concomitant Medications eCRF.

Table 4 Premedication for Pemetrexed

Premedication	Dose and Route	Timing
Folic acid	350–1000 μg PO	Once daily beginning at least 5–7 days before Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Vitamin B_{12}	1000 μg IM	Q9W beginning with the week preceding Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Dexamethasone (suggested)	4 mg PO	Twice daily the day before, the day of, and the day after pemetrexed administration

IM = intramuscular; PO = oral; Q9W = every 9 weeks

[redacted]. If the investigator prefers to treat a patient in Cohort A with adjuvant chemotherapy the reason must be documented in the patient's medical record and entered in the appropriate eCRF. If adjuvant chemotherapy is to be administered, treatment should begin within 28–72 days after surgery followed by PORT (if chosen) to begin within 21–60 days after adjuvant chemotherapy.

During post-operative adjuvant treatment, infusions will be administered in the following order (one regimen per patient). The choice of Cohort A (PD-L1 high) regimen is at the investigator's discretion for each patient.

Cohort A (PD-L1 high): The investigator will administer one of the regimens listed below.

- [redacted]

Cohort B (PD-L1 all comers): [redacted]

Cases of accidental overdose or medication error associated with atezolizumab or tiragolumab, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

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 10. Atezolizumab and tiragolumab infusions will be administered per the instructions outlined in Table 5.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

[redacted]. No dose modification for study treatment is allowed.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 4.6.1, Section 5.1.9, Appendix 11 (for chemotherapy), and Appendix 12 (for CPI).

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (see Section 3.1.1 for details). The dose of atezolizumab is fixed and is not dependent on body weight. Dose reductions are not allowed.

Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1, Section 5.1.9, and the Atezolizumab Investigator's Brochure. Guidelines for study drug administration in the context of management of specific adverse events are provided in Appendix 11.

4.3.2.2 Tiragolumab

Following the administration of atezolizumab and an observation period (see Table 5), patients will receive 600 mg tiragolumab administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.4.1). The tiragolumab dose is fixed and is not dependent on body weight. Dose reductions are not allowed.

Tiragolumab infusions will be administered per the instructions outlined in Table 5.

Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1 and Section 5.1.9. Guidelines for study drug administration in the context of management of specific adverse events are provided in Appendix 12.

Table 5 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab

Study drug	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion.	• If the patient experienced an IRR with any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic medications may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR or 60 (±15) minutes if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded during the infusion.

IRR = infusion-related reaction.

Table 5 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab (cont.)

Study drug	First Infusion	Subsequent Infusions
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous atezolizumab infusion well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to 30 minutes. • If the patient experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of atezolizumab.
Infusion of tiragolumab	• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within [redacted] minutes prior to the infusion. • Tiragolumab should be infused over [redacted] minutes. • Vital signs should be recorded every [redacted] minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of tiragolumab, [redacted] may be administered for subsequent doses, at the discretion of the investigator. • Vital signs should be recorded within [redacted] minutes prior to the tiragolumab infusion. • Tiragolumab should be infused over [redacted] minutes if the previous infusion was tolerated without an infusion-related reaction, or [redacted] minutes if the patient experienced an infusion-related reaction with the previous infusion. • Vital signs should be recorded during the infusion if clinically indicated.

IRR = infusion-related reaction.

Table 5 Administration of First and Subsequent Infusions of Atezolizumab and Tiragolumab (cont.)

Study drug	First Infusion	Subsequent Infusions
Observation period after infusion of tiragolumab	• After the infusion of tiragolumab, the patient begins a [redacted]-minute observation period. • Vital signs should be recorded at [redacted] minutes after the infusion of tiragolumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous infusion of tiragolumab well without infusion-associated adverse events, the observation period may be reduced to [redacted] minutes. • If the patient experienced an infusion-associated adverse event in the previous infusion, the observation period should be [redacted] minutes. • If clinically indicated, vital signs should be recorded at [redacted] minutes after the infusion of tiragolumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.

IRR = infusion-related reaction.

4.3.2.3 Atezolizumab and Tiragolumab Dose Delays

The following rules apply as long as neither atezolizumab nor tiragolumab has been permanently discontinued:

- Treatment cycles will normally begin with dosing of atezolizumab and tiragolumab on Day 1 of each 21-day cycle. If either study drug is delayed for a related toxicity, it is recommended that the other study drug is also delayed since the safety profiles for atezolizumab and tiragolumab are similar.
- In case of delays in dosing of one study drug for drug-related toxicity while the other study drug is given as planned, it is recommended that the study drug being delayed will be administered at the next scheduled infusion (i.e., at the next scheduled 21-day cycle).

4.3.2.4 Chemotherapy

Sites should adhere to the information below and to local prescribing information. In general, sites should also follow their institutional and local SOC for determining dose adjustments in the event of patient weight changes. If a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the chemotherapy regimen, both chemotherapy components should be held and if resumed, both should be resumed to remain synchronized.

Guidelines for dose modification and treatment interruption or discontinuation for chemotherapy are provided in Appendix 11.

Paclitaxel

[redacted]

Paclitaxel injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The infusion site should be closely monitored for possible infiltration during drug administration.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 μm. Use of filter devices such as IVEX-2® filters, which incorporate short inlet and outlet PVC–coated tubing, has not resulted in significant leaching of bis(2-ethylhexyl)phthalate.

Sites should follow their institutional SOC guidelines for determining the paclitaxel dose adjustments in the event of patient weight changes. For paclitaxel infusion, exceptions to the infusion time of 3 hours will be allowed for sites that have an institutional policy of infusing paclitaxel more quickly (over 90 minutes) or more slowly (up to 4 hours for the first infusion).

See the prescribing information for paclitaxel for more information.

Pemetrexed

Institutions should follow their standard administration procedures for pemetrexed. Administration of pemetrexed should be administered by IV infusion over at least 10 minutes. The premedication doses administered should be in compliance with the prescribing information (see Table 4). All patients eligible for pemetrexed therapy should avoid taking non-steroidal anti-inflammatory drugs with long drug-elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Gemcitabine

Gemcitabine should be administered by IV infusion over 30 minutes prior to carboplatin. Please refer to Table 3 for the appropriate gemcitabine dosing. Gemcitabine must be diluted prior to infusion. The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection, USP, without preservatives. The administration of gemcitabine should be done in accordance with local practice and the prescribing information.

See prescribing information for gemcitabine for more information.

Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of paclitaxel or pemetrexed administration, over 15–30 minutes to achieve an initial target area under the concentration-time curve (AUC) of 5 or 6 mg/mL/min (Calvert formula dosing) and with standard anti-emetic medications per local practice guidelines.

The carboplatin dose of AUC 5 or 6 mg/mL/min will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

$$\text{Total dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

Note: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this study, the GFR is considered to be equivalent to the creatinine clearance (CrCl). The CrCl is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} \quad (\times\ 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

[redacted]

If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \bullet \text{min/mL)} \ (\text{GFR} \times 25 \text{ mL/min})$$

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is $6 \times (125 + 25) = 900$ mg.
For a target AUC = 5, the maximum dose is $5 \times (125 + 25) = 750$ mg.
For a target AUC = 4, the maximum dose is $4 \times (125 + 25) = 600$ mg.

Cisplatin

Cisplatin should be administered by IV infusion, approximately 30 minutes after completion of the pemetrexed or per SOC at the institution. Patients must receive adequate antiemetic treatment and appropriate hydration prior to and after receiving cisplatin.

Refer to local clinical practice guidelines for further details.

4.3.3 Surgical Treatment Plan

An attending thoracic surgeon with experience in early-stage resectable NSCLC should evaluate patients at screening to determine surgical fitness and eligibility for surgical resection. Patients must be eligible for an R0 resection with curative intent at time of screening. The intent to downstage in order to render patient operable is not permitted.

At screening, patients must be confirmed for surgical fitness based on their PFTs as outlined in the inclusion criteria (see Section 4.1.1). ppoFEV_1 and ppoDL_{CO} should be calculated using the following methodology (Brunelli et al. 2013):

- [redacted]
- [redacted]

Patients must be reassessed after completion of neoadjuvant treatment and prior to surgery by the attending surgeon and medical oncologist. Preoperative evaluation, including, but not limited to, blood tests, coagulation, cardiac tests or PFTs (if indicated), anesthesia assessment, and other evaluation procedures, should be performed per local SOC.

The surgical procedure should be performed within [redacted] days after the pre-surgery visit as best as possible. [redacted]

[redacted]

The surgical procedure performed should be documented and reported on the eCRF. If, after neoadjuvant treatment or during the operation, the surgeon determines that the patient should not proceed with the planned surgery, the reason should be documented and reported in the eCRF as well.

After surgery and following review of the pathology report, the attending surgeon should complete the Thoracic Surgery Questionnaire.

4.3.4 Post-Operative Radiotherapy

[redacted]

[redacted]

4.3.5 Investigational Medicinal Product Handling 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 patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients 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 the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been 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 patients 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 the applicable Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.6 Continued Access to Atezolizumab and Tiragolumab

Currently, the Sponsor does not have any plans to provide Roche IMPs (atezolizumab and tiragolumab) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab and

tiragolumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- [redacted]

[redacted].

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion–associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 10).

4.4.2 Cautionary Therapy for Atezolizumab- and Tiragolumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to Appendix 12 for details).

4.4.2.2 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 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

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

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

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

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

All treatment visits must occur ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments should be performed on the day of the specified visit unless a time window is specified. Patients must be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Assessments scheduled on the day of study treatment administration should be performed prior to dosing, unless otherwise specified.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history

will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will 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.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status Scale at the timepoints specified in the schedule of activities in Appendix 1.

4.5.4 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 patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 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.

Refer to Table 5 and Appendix 1 for details on the measurements of vital signs during study treatment.

4.5.6 Tumor Response and Disease Status Follow-Up Evaluations

Screening assessments must include PET (whole body, or skull base to mid-thighs) with CT scans (with oral/IV contrast) of the chest and abdomen. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or a severe allergy), a non-contrast CT scan of the chest and abdomen may be performed along with the PET scan (whole body, or skull base to mid-thighs). A CT scan with contrast or magnetic resonance imaging (MRI) scan of the head must be done at screening to evaluate the presence of CNS metastasis in all patients to ensure eligibility (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm

or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

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

Tumor assessments performed as SOC prior to obtaining informed consent and within 35 days (for CT or MRI scan) or 42 days (for PET scan) prior to initiation of study treatment do not have to be repeated at screening.

All measurable and evaluable lesions should be assessed and documented at screening and re-assessed at each subsequent tumor evaluation during the neoadjuvant treatment phase. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 3) during the neoadjuvant treatment phase. Assessments should be performed by the same evaluator, if possible, to ensure consistency across visits. During the neoadjuvant treatment phase, patients will undergo tumor assessments at baseline and following the completion of Cycles 2 (within 7 days prior to Cycle 3 Day 1), and Cycle 4 (± 7 days of Cycle 4 Day 21), as per Appendix 1. [redacted]

After surgery and during the adjuvant treatment phase, disease status follow-up assessments will be performed in all patients (both cohorts) every 4 months from the day of surgery by chest CT with IV contrast (including the liver and adrenal glands) for the first year and then every 6 months in the second year. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed. Patients who have not experienced recurrence of disease will undergo disease status follow-up assessments every 6 months by chest CT scan with IV contrast (including liver and adrenals) during Years 3–5 post-surgery. Disease status follow-up assessments should occur within the allowed time-window of the scheduled follow-up evaluation. [redacted]

Disease recurrence after surgery should be confirmed pathologically and/or by unequivocal radiographic evidence. [redacted]

[redacted]

[redacted]

Tumor or disease status follow-up assessments should continue in patients who discontinue treatment early for reasons other than disease progression or recurrence (e.g., because of toxicity). In the absence of disease progression or recurrence, tumor or disease status follow-up assessments should continue in all patients, regardless of whether they start new anti-cancer therapy, until disease progression or recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis (see Appendix 1 and Appendix 2). Results must be reviewed prior to dosing:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR, and aPTT (see Appendix 1)
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. During the study, urine pregnancy tests will be performed at every cycle and after study treatment is discontinued (see Appendix 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (see Appendix 1).

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥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).
- Urinalysis: pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted

[redacted].

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis. Please refer to the laboratory or pathology manual for additional details (e.g., kits to be used, sample handling, etc.):

- Serum sample for analysis of autoantibodies (if deemed necessary by the sponsor in cases of an immune-related adverse event): anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Serum samples for atezolizumab and tiragolumab PK analysis through use of a validated assay
- Serum samples for assessment of anti-drug antibodies (ADAs) to atezolizumab and tiragolumab through use of a validated assay
- For patients with non-squamous NSCLC, if *EGFR* and/or *ALK* status is unknown, status must be assessed locally or at a central laboratory for determination of study eligibility (see Section 4.1.2 for exclusion criteria). [redacted]
- [redacted]

[redacted]

- Resected tumor and lymph node specimens obtained at surgery for pathologic response evaluation

  [redacted] Slides may be returned to the local site afterwards. [redacted]

- [redacted]

- [redacted]

[redacted]

Screening blood and tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

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

[redacted]

[redacted]

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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

4.5.8 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient 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 tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.9 Clinical Outcome Assessments

PRO instruments will be completed to more fully characterize the clinical profile of Atezo+Tira. In addition, PRO instruments will enable the capture of each patient's direct experience with Atezo+Tira.

PRO data will be collected through use of the following instruments: [redacted]

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

Paper versions of the PRO instruments will be self-administered by patients during the treatment period (see Schedule of Activities in Appendix 1). [redacted]

[redacted]

[redacted]

- [redacted]

[redacted] will be completed at baseline and at every treatment cycle through Cycle 4. The questionnaires will be collected at the pre-surgery visit and post-surgery visit. After surgery, from Cycle 5 on, the questionnaires will be completed at every other study treatment cycle until the study treatment discontinuation visit, and at the study treatment discontinuation visit (see Appendix 1).

Patients whose native language is not available with the questionnaires are exempted from completing all PRO assessments.

The Sponsor will not derive adverse event reports from PRO data (see Section 5.3.5.13).

4.5.9.2 Description of Clinical Outcome Assessment Instruments

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples may be collected for DNA extraction to enable [redacted] to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. DNA extracted from blood may be compared with DNA extracted from tissue to identify

somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for [redacted] or [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], this section of the protocol (Section 4.5.10) will not be applicable at that site.

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

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

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

Refer to Section 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Procedures

4.5.11.1 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at screening before treatment if clinically feasible, and at disease progression, as assessed by the investigator per RECIST v1.1, during neoadjuvant treatment. Patients may also undergo additional on-treatment biopsies at any other time at the investigator's discretion. Samples collected via resection (3 cores preferred, recommended minimum of 18-gauge needle, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are preferred. [redacted]. Fresh samples need to be processed and shipped immediately (refer to the laboratory manual for details).

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

[redacted]

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from [redacted].

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients 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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional 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 4.5.12.2) will not be applicable at that site.

4.5.12.3 Sample Collection

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

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

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

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

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

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

4.5.12.4 Confidentiality

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

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

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.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate 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 patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent 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.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients 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 or will no longer be linked to the patient. 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 patient 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 patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient 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 patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.12.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient 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.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to atezolizumab or tiragolumab, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event

  [redacted]

- Intolerable toxicity related to other components of the study treatment

  [redacted]

- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Unequivocal radiographic disease progression per RECIST v1.1 during the neoadjuvant treatment phase

- Pathologically confirmed or unequivocal radiographic evidence of disease recurrence during the adjuvant treatment phase

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

[redacted]

Patients will return to the clinic for a treatment discontinuation visit [redacted] days after the final dose of study treatment. The visit at which the disease assessment shows progressive disease or confirms disease recurrence may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or recurrence will continue to undergo tumor or disease status assessments as outlined in the schedule of activities (see Appendix 1).

[redacted]

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study (withdrawal

of consent), this request must be documented in the source documents and signed by the investigator. Patients who withdraw consent from participation in the study will not be replaced.

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

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on anticipated mechanism of action, results from nonclinical studies, published data on similar molecules, clinical experience with tiragolumab alone and in combination with atezolizumab in Phase I and II studies, and the clinical safety profile of atezolizumab. The anticipated important safety risks for atezolizumab, tiragolumab, and atezolizumab in combination with tiragolumab are outlined below (see Sections 5.1.1, 5.1.2, and 5.1.3, respectively). Refer to the Atezolizumab Investigator's Brochure and the Tiragolumab Investigator's Brochure for a complete summary of safety information for each study drug.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and tiragolumab will be performed in a monitored setting in which there is immediate access to trained personnel

and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 12. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

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

A JMC will periodically review safety data during the study (see Section 3.1.2).

5.1.1 Risks 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 lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 12 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Tiragolumab

[redacted] Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 12 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

5.1.2.1 Infusion-Related Reactions

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

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

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over [redacted] minutes followed by a [redacted]-minute observation period, and subsequent infusions as well as observation times may be shortened only if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Section 4.3.2 for detailed guidance on administration of tiragolumab in this study. Refer to Appendix 10 for guidance on anaphylaxis precautions, [redacted].

5.1.2.3 Lymphopenia

[redacted]

Patients with a lymphocyte count < 500 cells/μL will be excluded from this study (see Section 4.1.1), and CBCs will be monitored regularly during the study (see Appendix 1).

5.1.2.4 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 for induction of 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.

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 12.

5.1.2.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8+ T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

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

5.1.3 Risks Associated with the Combination of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and, there are known and potential for overlapping toxicities in patients 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 atezolizumab and tiragolumab, additional immune-mediated

adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with atezolizumab and tiragolumab 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 patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2). Patients previously treated with approved or experimental cancer immune therapies will also be excluded from participation in this study. [redacted]

5.1.4 Risks Associated with Cisplatin

Cisplatin is known to cause nephrotoxicity, neuropathies, ototoxicity and bone marrow suppression. Anaphylactic-like reactions to cisplatin have been reported. Nausea and vomiting may be intense and require adequate antiemetic treatment.

Patients will be monitored for cisplatin-related adverse events. For more details regarding the safety profile of cisplatin, refer to the cisplatin prescribing information.

5.1.5 Risks Associated with Carboplatin

Carboplatin is known to cause myelosuppression, nephrotoxicity, allergic reactions, neurologic toxicity, hemolytic-uremic syndrome, reversible posterior leukoencephalopathy syndrome, venoocclusive liver disease, and tumor lysis syndrome.

Patients will be monitored for carboplatin-related adverse events. For more details regarding the safety profile of carboplatin, refer to the carboplatin prescribing information.

5.1.6 Risks Associated with Pemetrexed

Pemetrexed is known to cause myelosuppression, nephrotoxicity, skin reactions, gastrointestinal toxicity, and cardiovascular toxicity.

Patients will be monitored for pemetrexed-related adverse events. For more details regarding the safety profile of pemetrexed, refer to the pemetrexed prescribing information.

5.1.7 Risks Associated with Paclitaxel

Paclitaxel is known to cause myelosuppression, alopecia, peripheral neuropathy, myalgia, arthralgia, diarrhea, nausea, and vomiting. Less commonly reported adverse events are hypersensitivity reactions, infections, bleeding, pseudomembranous colitis, mucositis, liver function test elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis.

For more details regarding the safety profile of paclitaxel, refer to the prescribing information for paclitaxel.

5.1.8 Risks Associated with Gemcitabine

Gemcitabine infusion times that are longer than 60 minutes or gemcitabine administration that occurs more frequently than once a week have been shown to increase toxicity. Pulmonary and cardiovascular toxicities have been reported with the use of gemcitabine. Capillary leak syndrome, including fatal cases, and posterior reversible encephalopathy syndrome with potentially severe consequences, have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Hemolytic-uremic syndrome and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Patients will be monitored for gemcitabine-related adverse events. For more details regarding the safety profile of gemcitabine, refer to the gemcitabine prescribing information.

5.1.9 Management of Adverse Events

5.1.9.1 Dose Modification, Treatment Interruption, or Treatment Discontinuation for Atezolizumab or Tiragolumab

Dose Modifications

There will be no dose modifications, including dose reductions, for atezolizumab or tiragolumab in this study.

Treatment Interruptions

Study treatment may be temporarily suspended 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 both study drugs, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both atezolizumab and tiragolumab.

After both study treatments have been discontinued, the patient will be monitored for safety and efficacy as defined in Section 4.6.1.

5.1.9.2 Management Guidelines for Atezolizumab- and Tiragolumab-Specific Adverse Events

Refer to Appendix 12 for details on the management of tiragolumab- and atezolizumab-specific adverse events. See Appendix 10 for precautions for anaphylaxis.

5.1.9.3 Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events for Chemotherapies

Refer to Appendix 11 for details on chemotherapy dose modifications, treatment delays, or treatment discontinuation and management of specific adverse events.

5.1.10 Potential Overlapping Toxicities

Based on nonclinical and/or clinical studies with atezolizumab or tiragolumab as a single agent, clinical data from studies with atezolizumab and tiragolumab as a combination therapy, and data from molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with atezolizumab plus tiragolumab. 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. The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus tiragolumab: immune-mediated pulmonary, hepatic, gastrointestinal, renal, endocrine, ocular, pancreatic, dermatologic, neurologic adverse events, as well as immune-mediated myocarditis, meningoencephalitis, and myositis.

Based on the clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with atezolizumab plus tiragolumab 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 patients.

The risk of overlapping toxicities between the CIT agents (atezolizumab and tiragolumab) and the chemotherapy agents (cisplatin, carboplatin, pemetrexed, paclitaxel, gemcitabine) is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin and gastrointestinal toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with pemetrexed and cisplatin/carboplatin (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tiragolumab and/or atezolizumab.

Toxicities should initially be managed according to the recommendations in Sections 5.1.1–5.1.8, Appendix 11, and Appendix 12 with dose holds and modifications (if applicable) applied to the component of the treatment judged to be the primary cause. If, in the opinion of the investigator, tiragolumab or atezolizumab is a potential inciting factor, the dose of tiragolumab and atezolizumab may be held for a maximum of [redacted] during post-surgery adjuvant treatment beyond the last infusion (see Appendix 12). Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be

acutely managed with systemic corticosteroids or TNF-α inhibitors. The Medical Monitor is available to advise as needed.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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 5.3.3); 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 learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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

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

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all 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].

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[redacted]

a [redacted]

b [redacted]

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 8):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 8 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/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 on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and 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, HLH, 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 Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF, as appropriate.

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF.

NCI CTCAE v5.0 and the [redacted] should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[redacted]

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient 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 learning that the event became serious; see Section 5.4.2 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 patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result 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., dosage 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

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result 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., dosage 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 (i.e., 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of

the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of ″non-small cell lung cancer″ 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 5.4.2). A JMC 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 5.6.

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Non–Small Cell Lung Cancer

Events that are clearly consistent with the expected pattern of progression or recurrence of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on radiographic evidence of disease progression (per RECIST v1.1) or evidence of radiographic disease recurrence after surgical resection of the primary tumor. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 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 5.2.2), 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., planned surgical resection or for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient 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 patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

  In some cases, a medication error may be intercepted prior to administration of the drug

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab and tiragolumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated atezolizumab and tiragolumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO–CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (on the PRO–CTCAE) with investigator reports of adverse

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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 becoming 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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. 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.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 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.

5.4.2.2 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]. In addition, adverse events of special interest will continue to 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 learning 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 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study, within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, and 6 months after the final dose of paclitaxel, pemetrexed, gemcitabine, carboplatin or cisplatin, whichever is later. 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 learning 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 patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient 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/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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study treatment, within 90 days after the final dose of tiragolumab, and 6 months after the final dose of chemotherapy (cisplatin, carboplatin, pemetrexed, paclitaxel or gemcitabine), whichever is later. 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 patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient 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.

5.4.3.3 Abortions

A spontaneous abortion 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 learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo-fetal 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 learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryo-fetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient 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 learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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 trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, 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.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (as defined in Section 5.3.1), 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, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/ Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

Drug	Document
Tiragolumab	Tiragolumab Investigator's Brochure
Atezolizumab	Atezolizumab 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.

A JMC will monitor the safety data during the study. An aggregate report of any clinically relevant safety signals that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a global phase II, open-label, multicenter study evaluating the safety and efficacy of neoadjuvant and adjuvant atezolizumab plus tiragolumab, with or without platinum-based chemotherapy, in patients with previously untreated, histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC.

Efficacy and safety analyses will be performed on all enrolled patients who have received at least one dose of the study drug, for each cohort.

6.1 DETERMINATION OF SAMPLE SIZE

The primary efficacy objective of this study is to evaluate MPR rate.

Cohort A has been closed early *due to the changing treatment landscape which includes chemotherapy as part of the approved treatment regimen in the perioperative setting (Section 1.3).*

*Cohort B will enroll a*pproximately [redacted] patients in this study. [redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed for each treatment cohort.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented. Summaries will be presented for overall population and for each treatment cohort.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of study drug, unless otherwise noted.

6.4 SAFETY ANALYSES

For each cohort, the safety analyses will include all enrolled patients who receive at least one dose of study treatment.

Study treatment exposure will be summarized, including treatment duration, dosage, and dose intensity.

Incidence and length of surgical delays, incidence of operative and post-operative complications and/or number of surgical cancellations related to study treatment will be evaluated for each cohort.

Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms. Severity for all adverse events will be graded by the investigator according to the NCI CTCAE v5.0, [redacted]. These summaries will be presented by treatment cohort. All adverse events will be summarized by treatment cohort and NCI CTCAE grade. [redacted]

In addition, the treatment-emergent adverse events leading to withdrawal of study treatment, leading to dose reduction or interruption, related to study treatment, severe adverse events (i.e., Grade ≥ 3 adverse events), fatal adverse events (i.e., Grade 5), serious adverse events, and adverse events of special interest will also be summarized. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ADA results, and changes in vital signs will be summarized by treatment cohort. Deaths and causes of deaths will be summarized.

6.5 EFFICACY ANALYSES

The efficacy analysis population will include all enrolled patients who received at least one dose of the study treatment.

6.5.1 Primary Efficacy Endpoint

MPR rate is defined as the proportion of patients who have achieved MPR and will be estimated for each treatment cohort in the efficacy analysis population. MPR is defined as $\leq$10% residual viable tumor at the time of surgical resection in the primary tumor, as assessed by *local* pathology laboratory. Patients who do not proceed to surgery are considered as non-responders for MPR. The two-sided 95% CI for MPR rate calculated using the Wilson score method will be reported.

6.5.2 Secondary Efficacy Endpoints

pCR rate is defined as the proportion of patients who have achieved pCR. pCR is defined as the absence of any viable tumor cells in both the primary tumor and all sampled lymph nodes at the time of surgical resection, as assessed by *local* pathology laboratory. pCR rate will be analyzed using the same statistical methodology as MPR rate for each treatment cohort for the efficacy analysis population.

Event-free survival (EFS) is defined as the time from first dose of the study drug to any of the following events, whichever occurs first: disease progression that precludes surgery, as assessed by the investigator; local or distant disease recurrence (including occurrence of new primary NSCLC); or death from any cause. Patients who have not experienced disease progression that precludes surgery, local or distant disease recurrence, or died at the time of analysis will be censored at the time of last tumor or disease follow-up assessment. Patients with no post-baseline tumor assessment will be censored at the date of first dose of the study drug. EFS will be evaluated using the Kaplan-Meier method for each treatment cohort for the efficacy analysis population.

[redacted]

These results may be reported separately from the Clinical Study Report.

6.6 PHARMACOKINETIC ANALYSES

Samples will be collected for PK analyses and to compare exposure in this study with that attained in previous studies. Serum concentrations of atezolizumab and

tiragolumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by cohort and cycle, when appropriate and as data allow. Individual and median serum concentrations of atezolizumab and tiragolumab will be plotted by cohort and day. Atezolizumab and tiragolumab concentration data may be pooled with data from other studies using an established population-PK model to derive PK parameters such as clearance, volume of distribution, and AUC, as warranted by the data. [redacted].

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

The numbers and proportions of treatment-emergent ADA-positive patients and ADA-negative patients for both atezolizumab and tiragolumab will be summarized by cohort.

The relationship between ADA status and safety, efficacy, and PK endpoints may be analyzed and reported via descriptive statistics.

[redacted]

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche 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.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their

consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for 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. Investigators are

also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, 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 other summary reports will be provided upon request (see Section 9.6).

8.5 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 course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient 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.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed.

Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 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 35 sites globally will participate to enroll approximately [redacted] patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A JMC will monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority database for public access, as required by local regulation, and will be made available 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/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any

country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center 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. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	Within [redacted] days r last neoadjuvant treatment dose	Within [redacted] days fter Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] Days after Final Dose or Last Visit	Every [redacted] Months [redacted]
Informed consent(s) [a, i]	x								
Surgical Feasibility Form[j]	x								
ALK and/or *EGFR* assessment (if status is unknown) [k]	x								
Tumor tissue and lymph node sample	x [l]				x[m]				
Demographics (age, sex, and self-reported race/ethnicity)	x								
Medical history and baseline conditions	x								

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Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	Within [redacted] days after last neoadjuvant treatment dose	Within [redacted] days after Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] Days after Final Dose or Last Visit	Every [redacted] Months [redacted]
Thoracic surgery evaluation	x			x					
Neoadjuvant Treatment Administration [n] **Cohort A (PD-L1 high):** [redacted] **Cohort B (PD-L1 all comers):** [redacted]			X						
Pathological response assessment					x				
Thoracic Surgery Questionnaire					*x*				

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Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	Within [redacted] days after last neoadjuvant treatment dose	Within [redacted] days after Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] after Final Dose or Last Visit	Every [redacted] Months [redacted]
Adjuvant Treatment Administration [n, o] **Cohort A (PD-L1 high):** [redacted] **Cohort B (PD-L1 all comers):** [redacted]							x		
Patient-reported outcomes [p]			Day 1 only of each cycle	x		x	Day 1, Cycle 5 and Day 1, every other cycle thereafter	x	

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Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	[redacted] days after last neoadjuvant treatment dose	[redacted] days after Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] Days after Final Dose or Last Visit	Every [redacted] Months [redacted]
Vital signs [q]	x		X				x	x	
Weight	x		X				x	x	
Height	x								
Complete physical examination [r]	x								
Limited physical examination [s]			X[w]				x		
Pulmonary function test [t]	x			x					
ECOG Performance Status	x								
ECG [u]	x		X				x		
Hematology [v]		x	x [w]				x	x	
Chemistry [x]		x	x [w]				x	x	
Pregnancy test [y]		x	X[w]				x	x [y]	x [y]
Coagulation (INR, aPTT)		x						x	
TSH, free T3 (or total T3), free T4 [z]	x		x [w. z]				x [z]	x	

Appendix 1: Schedule of Activities

Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	[redacted] days after last neoadjuvant treatment dose	[redacted] days after Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] Days after Final Dose or Last Visit	Every [redacted] Months [redacted]
[redacted] [aa]	x								
Urinalysis [bb]	x		x [w, bb]				x [bb]		
Blood for serum, plasma and PBMC preparation[cc]			Refer to Appendix 2						
[redacted]			Refer to Appendix 2						
			At Cycle1 Day1 or as soon as possible after enrollment, during the conduct of the clinical study						
	x [ee]								
Tumor biopsy at the time of disease progression/recurrence			x [ff, gg]				x [gg]	x [gg]	
Tumor response and disease status FU assessments	x [hh]		x [i]				x [jj]	x [jj]	x [jj]
Concomitant medications [kk]	x		x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Assessment	Screening [a]		Neoadjuvant Tx (21-Day Cycles) (Cycles 1–4)	Pre-Surgery Visit [d]	Surgery [e]	Post-Surgery Visit [f]	Adjuvant Tx (21-Day Cycles) (Cycles 5+)	Tx DC [h]	Survival Follow-Up
	Days –42 to –1	Days –14 to –1	Day 1 (± 3 days) [b] Gemcitabine: Day 8 (± 1 day)[c]	Within [redacted] days after last neoadjuvant treatment dose	Within [redacted] days after Pre-Surgery Visit	14–21 days after surgery	Day 1 (± 3 days) Gemci-tabine: Day 8 (± 1 day)[g]	[redacted] Days after Final Dose or Last Visit	Every [redacted] Months [redacted]
Adverse events [ll]	x		x	x		x	x	x	x
[redacted]	x		Any time during study treatment, or survival FU (at investigators discretion)						
Survival FU and anti-cancer treatment									x [nn]

ADA = anti-drug antibody; *ALK* = anaplastic lymphoma kinase ; CT = computed tomography (scan); DC = discontinuation; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; FU = follow-up; [redacted] MPR = major pathological response; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PBMC = peripheral blood mononuclear cell; pCR = pathological complete response; PCR = polymerase chain reaction; PET = positron emission tomography; PFT = pulmonary function test; PK = pharmacokinetic; PORT = post-operative radiotherapy; PRO = patient-reported outcome; Q3W = every 3 weeks; [redacted] RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard or care; Tx = treatment.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 4 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Cycle 1 Day 1 should occur no later than five days after enrollment.

[c] Neoadjuvant gemcitabine will be administered only to patients in Cohort B (PD-L1 all-comer) who are receiving *carboplatin* with gemcitabine in addition to atezolizumab plus tiragolumab. Adjuvant gemcitabine will be administered only to patients in Cohort A receiving *carboplatin* with gemcitabine.

[d] The pre-surgery visit should occur within [redacted] days after last dose of neoadjuvant treatment, and associated assessments should be completed in accordance with local practice.

[e] Surgery should be scheduled within [redacted] days after the pre-surgery visit or as close as possible per clinical judgement of both the attending surgeon and medical oncologist. Any anticipated delay beyond this window should be discussed with the Medical Monitor. See Section 4.3.3 for guidance on surgical treatment plan.

[f] The post-surgery visit should occur within [redacted] days after surgery. The medical oncologist and/or attending surgeon will meet with the patient to assess their well-being and inform the patient of their post-surgery treatment plan for the study (i.e., treatment assignment or if PORT is deemed necessary).

[g] Adjuvant gemcitabine will be administered only to patients in Cohort A receiving *carboplatin* with gemcitabine.

[h] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than [redacted] days after the last does of study treatment. The visit at which response assessment shows disease progression or recurrence may be used as the Treatment discontinuation visit.

[i] Informed consent must be documented before any study-specific screening procedure is performed, [redacted].

[j] [redacted]

[k] For patients with non-squamous or mixed histology with observed non-squamous component that have unknown EGFR and/or ALK status, if local testing results are not available, testing must be completed centrally to confirm eligibility.

[l] Archival or fresh tumor biopsy sample suitable for central PD-L1 testing is required, [redacted] Samples and associated pathology report should be submitted during screening and at least 2 weeks prior to study enrollment. For patients who have unknown *EGFR* or *ALK* status will be required to be tested at screening. *EGFR* and/or *ALK* status may be assessed locally or at a central laboratory. *EGFR* status assessed locally must be performed on tissue or cytology using a validated health authority approved test (or CE-marked test in the EU) that detects mutations in exons 18–21. If samples are submitted for central *EGFR* and/or *ALK* test, [redacted]. Refer to Section 4.5.7 for tissue sample requirements.

[m] Tumor tissue and lymph node tissue obtained from surgical resection is required for pathological response analysis. [redacted] Refer to Section 4.5.7 for tissue sample requirements.

[n] The initial infusion of atezolizumab *or tiragolumab* will be delivered over [redacted] minutes. Subsequent infusions will be delivered over [redacted] minutes if the previous infusion was tolerated without infusion-associated adverse events, or [redacted] minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[o] Patients enrolled to Cohort A (PD-L1 high) will receive adjuvant treatment with Atezo + Tira Q3W for 16 cycles, or platinum based chemotherapy for 4 cycles, and will be scheduled for disease FU assessments. Patients enrolled to Cohort B will receive adjuvant treatment with Atezo + Tira Q3W for 16 cycles and will be scheduled for disease FU assessments as well. If PORT is required, Cycle 5 will begin after PORT is completed. See Section 4.5.4 for guidance regarding PORT.

[p] PRO assessments ([redacted]) are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, lab results or health record, before administration of study treatment, and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. During the neoadjuvant treatment phase, PRO assessments will be administered on Day 1 of each cycle only. PRO assessments will be collected at the pre-surgery visit and post-surgery visit. During the adjuvant treatment phase, PRO assessments will be administered on Day 1 of Cycle 5 and Day 1 of every other cycle thereafter. For patients who are unable to come to the clinic due to government restrictions or safety considerations and continuing to receive treatment, PROs may be completed via a telephone call; source documentation sufficient to pass an audit should be obtained which includes, among other information, that the questionnaires were administered via telephone because of government restrictions or safety considerations.

[q] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (±10) minutes after the infusion.

[r] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[s] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints.

[t] Pulmonary function tests (PFTs) must have been performed within 6 months of planned resection and repeated at screening (only if clinically indicated), and should include lung volumes, spirometry, and a diffusion capacity. PFTs must be repeated at screening if performed before 6 months of planned resection or have never been performed. Abnormal PFTs may be further evaluated with quantitative ventilation/perfusion scanning or cardiopulmonary exercise testing. Repeat PFTs should be performed at the pre-surgery visit after completion of neoadjuvant treatment, if clinically indicated, or as part of local institutional pre-surgery workup. PFT values must meet criteria outlined in Section 4.1.1

[u] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[v] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Hematology labs should also be performed prior to administration of gemcitabine on Day 8.

[w] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[x] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. Chemistry panel assessments should also be performed prior to administration of gemcitabine on Day 8.

[y] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. After screening, urine pregnancy tests will be performed at every cycle in the neoadjuvant phase, during every cycle in the adjuvant treatment phase and at the treatment discontinuation visit. After the treatment discontinuation visit, a urine pregnancy test will be performed at either 6 months after the final dose of chemotherapies, 90 days after the final dose of tiragolumab, or 5 months after the final dose of atezolizumab, whichever is later. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[z] TSH, free T3 (or total T3 at sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and 4 for both cohorts in the neoadjuvant phase and Cycles 5, 9, 13, 17, and 20 only for patients receiving Atezo + Tira in the adjuvant phase.

[aa] [redacted]

[bb] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis should be performed as clinically indicated during study treatment.

[cc] Serum samples collected for the assessment of pharmacokinetics, ADAs, or biomarkers at baseline and on Day 1 of Cycle 1 prior to the first dose of study treatment may be used for autoantibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment. See Appendix 2 for detailed schedule.

[dd] A blood sample for the RBR will be collected predose on Cycle 1, Day 1. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[ee] [redacted]

[ff] Patients will undergo an optional tumor biopsy, if clinically feasible, at the time of first evidence of radiographic disease progression per RECIST v1.1 (optional) during the neoadjuvant treatment phase. Collection should include involved and non-involved lymph nodes, if available. See Section 4.5.7 for tissue sample requirements.

[gg] Patients will undergo a mandatory tumor biopsy, if clinically feasible, during the adjuvant treatment or follow-up phase for pathological confirmation of disease recurrence, [redacted] Biopsies should be performed prior to the next anti-cancer therapy. Collection should include involved and non-involved lymph nodes, if available. See Section 4.5.7 for tissue sample requirements.

[hh] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as SOC prior to obtaining informed consent and within 35 days (for CT or MRI) or 42 days (for PET) prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include PET scan (whole body, or skull base to mid-thighs) and CT scan (with oral or IV contrast) of the chest, abdomen, and head (See Section 4.5.6). A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest and

abdomen may be performed along with the PET (whole body, or base of skull to mid-thighs). A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[ii] Patients will undergo tumor assessments after completion of Cycle 2 (within 7 days prior to Cycle 3 Day 1), and Cycle 4 (+/- 7 days of Cycle 4 Day 21), following treatment initiation per RECIST v1.1 during the neoadjuvant treatment phase. All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). [redacted]

[jj] Patients will undergo scheduled disease FU assessments on chest CT scans (including liver and adrenal glands) (with contrast unless contraindicated) every 4 months after surgery for the first year, and every 6 months in the second year. Patients who have not experienced recurrence of disease will undergo disease FU assessments every 6 months by chest CT (including liver and adrenal glands) Years 3–5. If a disease FU assessment suggests potential disease recurrence, the event should be confirmed pathologically and/or by unequivocal radiographic evidence. [redacted]

In the absence of disease recurrence, disease FU assessments are to continue according to schedule in patients who discontinue adjuvant treatment with Atezo + Tira for reasons other than recurrence of disease. Disease FU assessments should occur within the allowed time window regardless of treatment delays. [redacted]

[kk] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

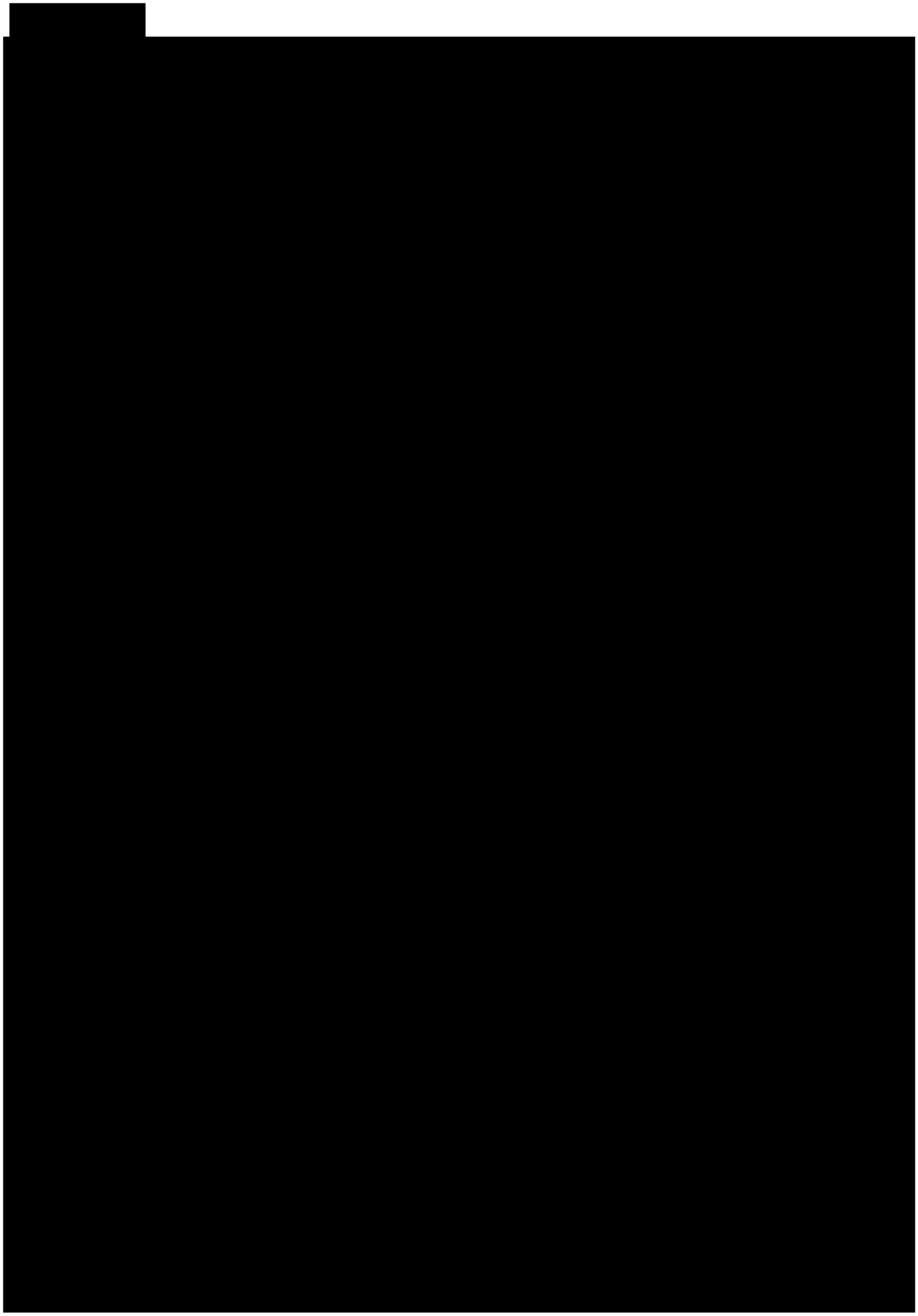
[ll] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted], and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted] After this period, all deaths, regardless of cause, should be reported. In addition, the

Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[mm] [redacted]

[nn] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every [redacted] months ([redacted] days) or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[redacted]



Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly- identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of nontarget disease or new

lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or nonmeasurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 4
AJCC/UICC Non-Small Cell Lung Cancer Staging, 8th Edition

American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) non–small cell lung cancer (NSCLC) Staging, 8th edition.

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	Single extrathoracic metastasis[e]
M1c	Multiple extrathoracic metastases in one or more organs

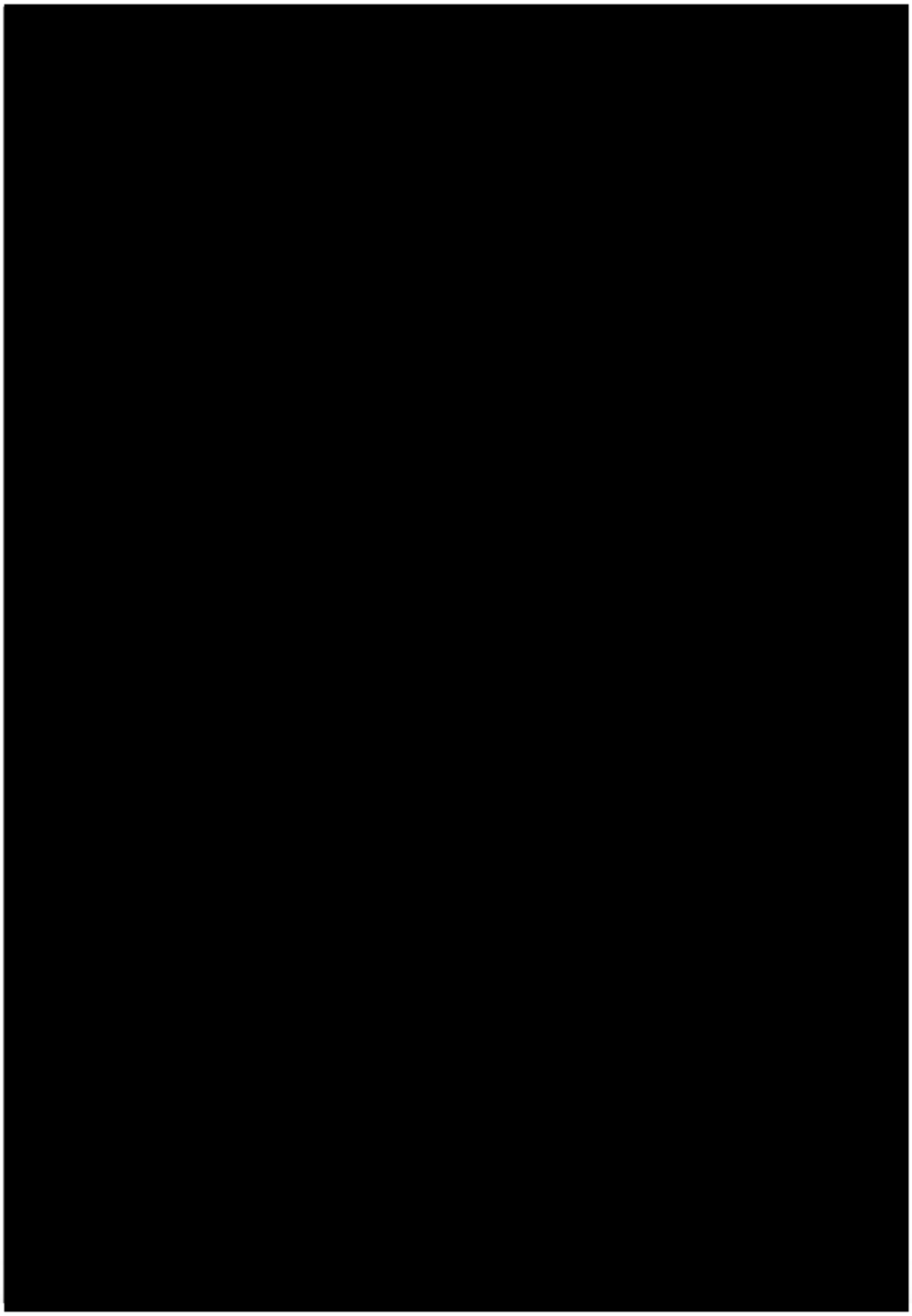
Note: Changes to the seventh edition are in bold.
[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.

Appendix 4: AJCC/UICC Non Small Cell Lung Cancer Staging, 8th Edition

		N categories			
		Overall stage			
Descriptor in 7th edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a]Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

[redacted]



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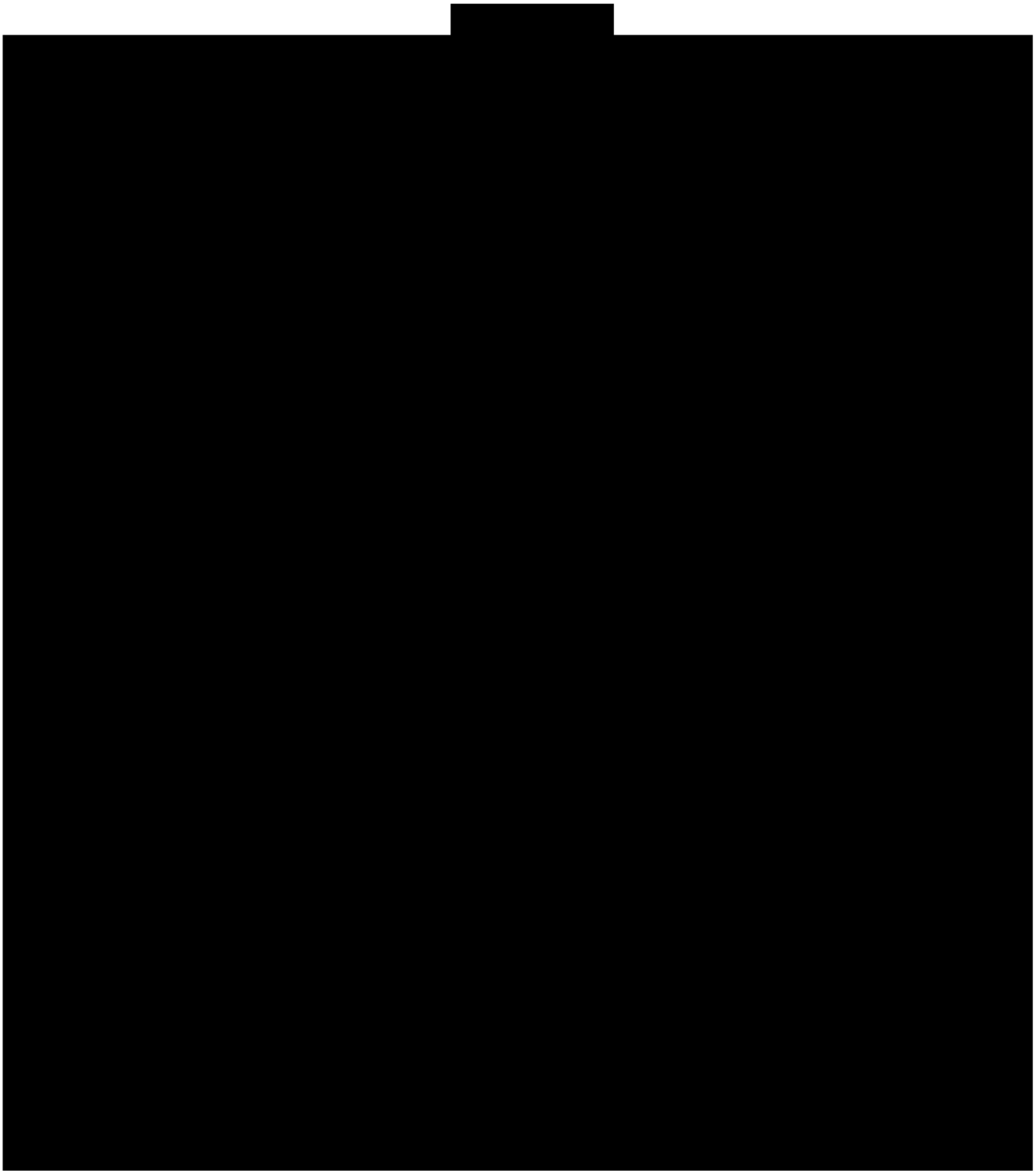

Appendix 9
Preexisting Autoimmune Diseases and Immune Deficiencies

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 or patients with controlled Type 1 diabetes mellitus who are on an insulin regimen 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 10
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 infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 11
Guidelines for Management of Adverse Events Associated with Chemotherapy

This appendix provides guidelines for the management of patients who experience adverse events associated with platinum-based chemotherapy (see Table 1–Table 12). Appendix 12 describes risks associated with atezolizumab and tiragolumab and provides guidelines for management of patients who experience atezolizumab- and tiragolumab-associated infusion-related reactions (IRRs) and immune-mediated adverse events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, myocarditis, pancreatic, dermatologic, neurologic, meningoencephalitis, renal, myositis, and hemophagocytic lymphohistiocytosis).

DOSE MODIFICATIONS

Dose modifications for cisplatin, carboplatin, pemetrexed, paclitaxel, and gemcitabine are permitted for toxicity according to the prescribing information and local standard of care. When a treatment cycle is delayed or interrupted because of toxicity resulting from any component of the regimen, all study drugs should generally be withheld and resumed together to remain synchronized. [redacted]

CISPLATIN DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Treatment with cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 63 days due to toxicities.

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2015; NCCN 2020). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 1).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 1 Cisplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Cisplatin Dose
ANC $<$ 500 cells/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 50,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<$ 1000/μL plus fever of $\geq$ 38.5°C	75% of previous dose

[a] Nadir of prior cycle.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment then can be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicity

If a patient develops a non-hematologic toxicity (see Table 2), cisplatin should be withheld for up to 63 days until resolution to equal or less than the patient's baseline (or Grade $\leq$ 1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 2.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics.

Table 2 Cisplatin Dose Modification for Non-Hematologic Toxicities (Excluding Neurotoxicity)

Toxicity	Cisplatin Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose
Grade 3 or 4 nausea/vomiting [a]	75% of previous dose
Any other Grade 3 or 4 toxicity	75% of previous dose

[a] Despite the use of anti-emetics.

Nephrotoxicity

Creatinine clearance (CrCl) must be ≥ 60 mL/min prior to the start of any cycle. If there is a decrease in CrCl between cycles, but the CrCl is still above 60 mL/min at the time of the next cycle, the treating physician should use his or her clinical judgment regarding continuing cisplatin, dose reduction, or delaying the cycle. If a patient's CrCl value has not returned to 60 mL/min within 63 days following the last cisplatin administration, the patient must be discontinued from cisplatin.

Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 3. For a Grade 3 or 4 neurotoxicity, cisplatin should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

Table 3 Cisplatin Dose Modification for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	75% of previous dose
Grade 3 or 4 neurotoxicity	50% of previous dose or permanent discontinuation

If the patient develops ototoxicity, subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits (http://www.drugs.com/pro/platinol.html). Refer to Table 3 for dose modification.

CARBOPLATIN DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Treatment with carboplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 63 days due to toxicities.

Additional guidance has been provided regarding recommended dose reductions, holds, and discontinuations of study treatment for toxicities and/or to comply with the prescribing information (see Section 4.3.2).

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL, and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2015; NCCN 2020). Upon recovery, dose adjustments at the

start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 4).

Table 4 Carboplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Carboplatin Dose
ANC $<$ 500 cells/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 50,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<$ 1000/μL plus fever of $\geq$ 38.5°C	75% of previous dose

[a] Nadir prior cycle.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment will then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table 5), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$ 1 if patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 5 provides the relevant dose adjustments for non-hematologic toxicities.

Table 5 Carboplatin Dose Modification on the Basis of Non-Hematologic Toxicities in the Preceding Cycle

Toxicity		Adjusted Carboplatin Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea/vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetics.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics. For a Grade 3 or 4 neurotoxicity, carboplatin should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

PEMETREXED DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

The dose modification guidelines are applicable for pemetrexed used as a single agent or in combination with cisplatin or carboplatin.

Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 63 days due to toxicities (see Table 7).

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL, and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2015; NCCN 2020). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see Table 6).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 6 Pemetrexed Dose Modification for Hematologic Toxicities

Toxicity [a]	Pemetrexed Dose
ANC $<$ 500 cells/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 50,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose

[a] Nadir of prior cycle.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment then can be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicity

At the start of each cycle, the CrCl must be $\geq$ 45 mL/min. For enrollment and dosing decisions, CrCl will be estimated using the original, weight-based Cockcroft and Gault formula or measured using the appropriate radiolabeled method (51Cr-EDTA or Tc99m-DTPA) to determine the glomerular filtration rate (GFR). The method of CrCl assessment used at baseline should be used throughout the study.

If a patient develops a non-hematologic toxicity (Table 7), pemetrexed should be withheld for up to 63 days until resolution to equal or less than the patient's baseline (or Grade 1 or better if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 7. For a Grade 3 or 4 neurotoxicity, pemetrexed should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on the investigator's clinical judgment).

Table 7 Pemetrexed Dose Modification for Non-Hematologic Toxicities

Toxicity	Pemetrexed Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose
Neurotoxicity	
Grade 2	75% of previous dose
Grade 3 or 4	50% of previous dose or permanent discontinuation
Any other Grade 3 or 4 toxicities	75% of previous dose

Treatment Delays Caused by Insufficient Folic Acid or Vitamin B12 Supplementation

Cycle 1 should not be started until both of the following requirements are met:

- The patient has taken folic acid for at least 5 days immediately preceding the first dose of pemetrexed, and
- The patient has received a vitamin B_{12} injection (which can be given on Cycle 1, Day 1)

Delay subsequent cycles until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the subsequent cycle.

For more details regarding pemetrexed dose modification, see the prescribing information for pemetrexed.

PACLITAXEL DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

The dose modification guidelines are applicable for paclitaxel used as a single agent or in combination with carboplatin.

Dose reductions, holds, and discontinuations for each study drug may be made as outlined below. The investigator may use discretion in modifying or accelerating the dose modification guidelines described below, depending on the severity of toxicity and an assessment of the benefit versus the risk for the patient, with the goal of maximizing patient compliance and access to supportive care.

Investigators should be vigilant and alert to early and overt signs of myelosuppression/infection/febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

Dose modifications of carboplatin and paclitaxel are allowed as described in the following sections.

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL, and the platelet count must be ≥100,000 cells/μL. Treatment may be delayed for up to 63 days from the last dose to allow sufficient time for recovery. Growth factors may be used in lieu of a dose reduction for neutropenic fever or Grade 4 neutropenia in accordance with ASCO and NCCN guidelines (Smith et al. 2015; NCCN 2020). Upon recovery, dose adjustments at the start of a subsequent cycle will be based on the lowest platelet and neutrophil values from the previous cycle (see Table 8 and Table 9).

Table 8 Dosing Based on ANC and Febrile Neutropenia—Paclitaxel and Carboplatin

	Dose of Paclitaxel and Carboplatin ANC (Day 1 of Each Cycle)	
	<1500/μL	≥1500/μL
Febrile neutropenia (regardless of duration)	0	Paclitaxel 150 mg/m^2 Carboplatin AUC =4.5 mg/mL/min

AUC=area under the concentration–time curve.

Table 9 summarizes dose modifications based on platelet count.

Table 9 Dosing Based on Nadir Platelet Count—Paclitaxel and Carboplatin

	Dose of Paclitaxel and Carboplatin Platelets (Day 1 of each cycle)	
Nadir of Last Course	<100,000/μL	≥100,000/μL
<25,000/μL or <50,000/μL with bleeding or requiring transfusion	0	Paclitaxel=150 mg/m^2 Carboplatin AUC=4.5 mg/mL/min

AUC=area under the concentration–time curve.

All dose reductions for the first episode of neutropenic fever or thrombocytopenia (platelet count <25,000/μL or <50,000/μL with bleeding or that requires transfusion) are permanent. If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, another 25% dose reduction of carboplatin and paclitaxel is recommended. Patients who require a third dose reduction will immediately discontinue chemotherapy.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Treatment should be delayed for up to 3 weeks until the Day 1 ANC is ≥1500/μL, and the platelet count is ≥100,000/μL. However, if the counts have not recovered in 3 weeks, the patient's chemotherapy will be dose reduced, withheld until adequate neutrophil recovery, or discontinued, according to physician judgment and local standard practice. If chemotherapy is withheld longer than 63 days from the last dose, all chemotherapy should be discontinued.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's institution's guidelines.

Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 10 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 10 Carboplatin and Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity		Adjusted Carboplatin Dose as % of Previous Dose [a]	Adjusted Paclitaxel Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75	75
Oral mucositis/stomatitis	Grade 3 or 4	*100*	*50*
Nausea/vomiting	Grade 3 or 4	75	75

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] And per investigator discretion.

Nausea and/or vomiting should be controlled with adequate anti-emetic medications. If Grade 3 or 4 nausea/vomiting occurs despite the use of anti-emetic medications, the dose should be reduced by 25% for the next course. If tolerated, the dose should be increased back to 100% as soon as possible.

If, on Day 1 of any treatment cycle, the patient has oral mucositis/stomatitis, the treatment should be withheld until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 3 weeks, the patient's chemotherapy will be discontinued. If acute Grade 3 oral mucositis occurs at any time, 75% of the dose should be given when the oral mucositis is completely cleared. This is a permanent dose reduction.

Hepatic Toxicity (Paclitaxel Only)

No dose adjustment is required in patients with mild hepatic impairment. For patients who develop hepatic toxicity, paclitaxel dose should be withheld until liver function tests (LFTs) resolve to Grade 1 or better prior to subsequent dosing. If paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the paclitaxel is resumed.

The recommendations for paclitaxel dose reduction based on elevated LFTs are provided in Table 11.

Table 11 Dose Modifications for Paclitaxel for Hepatic Toxicity

SGOT (AST) Levels		Bilirubin Levels	Paclitaxel Reduction from Starting Dose
$<10\times$ ULN	AND	$\leq 1.25\times$ ULN	No change
$<10\times$ ULN	AND	$1.26-2.0\times$ ULN	25%
$<10\times$ ULN	AND	$2.01-5.0\times$ ULN	50%
$>10\times$ ULN	OR	$>5.0\times$ ULN	Discontinue paclitaxel [a]

ULN = upper limit of normal.

Note: Recommendations for paclitaxel dose adjustments are extrapolated from dose adjustments for patients with hepatic impairment at baseline.

[a] Patients with AST $>10\times$ ULN or bilirubin $>5.0\times$ ULN were excluded from clinical studies for lung cancer.

If paclitaxel is withheld, hepatic values must recover to Grade ≤ 1 within 3 weeks or the patient's paclitaxel treatment will be discontinued. No dose reductions for carboplatin will be made for hepatic toxicity.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement. All study treatment should be discontinued if the disease under investigation has progressed.

Cardiovascular Toxicity (Paclitaxel Only)

Cardiac rhythm disturbances have occurred infrequently in patients treated with paclitaxel in clinical studies; however, most patients were asymptomatic, and cardiac monitoring is not required. Transient asymptomatic bradycardia has been noted in as many as 29% of patients. More significant atrioventricular block has rarely been noted. Cardiac events should be managed as follows:

- Asymptomatic bradycardia: no treatment required
- Symptomatic arrhythmia during infusion: Stop paclitaxel infusion, manage arrhythmia according to standard practice. Paclitaxel treatment will be discontinued.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or requires fluid replacement): Stop paclitaxel infusion. Perform an ECG. Give IV diphenhydramine and dexamethasone if hypersensitivity is considered. Also consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. Paclitaxel treatment will be discontinued, and cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought.

Neurologic Toxicity (Paclitaxel Only)

The dose of paclitaxel should be modified as follows for sensory neuropathy.

Table 12 Paclitaxel Dose Modification for Neurologic Toxicity

Toxicity	Paclitaxel Dose Modification
Grade 0	None
Grade 1	None
Grade 2	Withhold treatment until patient recovers to Grade 1 toxicity, then resume treatment at a 25% reduction.
Grade 3 or worse	Withhold treatment until patient recovers to Grade 1 toxicity, then resume treatment at a 50% reduction.

Dose modifications made for neurotoxicity are permanent. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's paclitaxel treatment will be discontinued.

Allergic Reaction and Hypersensitivity (Paclitaxel Only)

Caution: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but the administration of prophylactic medication (see below) and intensive monitoring of vital signs is recommended.

- Mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No treatment required.
- Moderate symptoms: Stop paclitaxel infusion. Give IV diphenhydramine 25–50 mg and IV dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hr for 15 minutes, then 40 mL/hr for 15 minutes, then

if no further symptoms, at full-dose rate until infusion is complete. If symptoms recur, stop paclitaxel infusion. Paclitaxel treatment will be discontinued.

- Severe life-threatening symptoms: Stop paclitaxel infusion. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel treatment will be discontinued.

Moderate or severe hypersensitivity reactions should be recorded as an adverse event.

Other Toxicities

For any Grade 3 or 4 toxicities not mentioned above, carboplatin or paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment should then be resumed at 75% dose (permanent dose reduction) for Grade 3 toxicities and 50% of dose (permanent dose reduction) for Grade 4 toxicities. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

For guidelines on the dosing of other study drugs when carboplatin or paclitaxel are withheld, see Section 5.1.9.

GEMCITABINE DOSE MODIFICATIONS, TREATMENT DELAYS OR TREATMENT DISCONTINUATION, AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

The dose modification guidelines for gemcitabine are provided below. *Refer to local label for gemcitabine and chemotherapy combination dose modification guidelines.*

Treatment with gemcitabine should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions, or if treatment is delayed for more than 21 days due to toxicities.

Hematologic Toxicities

At the start of each cycle, the ANC must be $\geq$1500 cells/μL and the platelet count must be $\geq$100,000 cells/μL. Gemcitabine dose modifications for hematologic toxicity should be on the basis of the granulocyte and platelet counts taken on Days 1 and 8 of therapy (see Table 13 and Table 14). Patients receiving gemcitabine should be monitored prior to each dose with a full blood count, including differential and platelet counts. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2015; NCCN 2020). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest (nadir) platelet and neutrophil values from the previous cycle (see Table 13).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 13 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 1

Toxicity [a]	Gemcitabine Dose
ANC > *10*00/μL and platelets ≥*10*0,000/μL	*100*% of previous dose
ANC 500-999/μL OR platelets 50,000-99,999/μL	75% of previous dose
ANC <*500*/μL *OR platelets* <*50,000/μL*	*Hold*

[a] Nadir of prior cycle.

Table 14 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 8

Absolute Granulocyte Count		Platelet Count	Percent of Gemcitabine Dose on Day 1
> 1*5*00/μL	and	> 100,000/μL	100
*10*00–*1500*/μL	or	*75*,000–*100,000*/μL	75
<*10*00/μL	or	<*75*,000/μL	*Omit dose*

Note: Omitted Day 8 doses of gemcitabine will not be made up. Day 8 dose adjustment for neutropenia and/or platelets is not a permanent dose reduction.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicities

In general, for Grade 3 or 4 non-hematologic toxicities, gemcitabine should be withheld or the dose reduced by 50%, according to physician judgment.

Permanent discontinuation should be considered for any of the following events:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 15 provides dose modification guidelines for non-hematologic toxicities.

Table 15 Gemcitabine Dose Modifications, Treatment Delays, or Treatment Discontinuation and Patient Management for Grade 2–4 Non-Hematologic Toxicities

	Grade 2	Grade 3	Grade 4
First appearance	Interrupt treatment until resolved to Grade 1 or better, then continue at same dose with prophylaxis where possible.	Interrupt treatment until resolved to Grade 1 or better, then continue at 75% of original dose with prophylaxis where possible.	Discontinue treatment unless investigator considers it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 1 or better.
Second appearance of same toxicity	Interrupt treatment until resolved to Grade 1 or better, then continue at 75% of original dose.	Interrupt treatment until resolved to Grade 1 or better, then continue at 50% of original dose.	
Third appearance of same toxicity	Interrupt treatment until resolved to Grade 1 or better, then continue at 50% of original dose.	Discontinue treatment permanently.	
Fourth appearance of same toxicity	Discontinue treatment permanently.		

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Appendix 12
Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

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

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

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

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab and tiragolumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

- The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab and tiragolumab. [redacted]

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. [redacted]

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients 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, chronic obstructive pulmonary disease, or pulmonary

hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

d

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

d

HEPATIC EVENTS

Patients 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 2.

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	• [redacted] •
[redacted]	[redacted]

[redacted]

a [redacted]

b

c

Table 2 Management Guidelines for Hepatic Events (cont.)

[redacted]

a [redacted]

b

c

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 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 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
[redacted]	• [redacted]

GI = gastrointestinal.

a [redacted]

b

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

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

GI = gastrointestinal.

a [redacted]

b

c

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

Event	Management
[redacted]	• [redacted]

GI = gastrointestinal.

[redacted]

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients 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. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and

magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	
[redacted]	
[redacted]	

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

a [redacted]

b

c

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

a [redacted]

b

c

IMMUNE-MEDIATED CARDIAC EVENTS

[redacted] Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

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

[redacted]

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

[redacted]

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[redacted]	[redacted]
or	
[redacted]	

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

INFUSION-RELATED REACTIONS

[redacted]

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with tiragolumab 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 or atezolizumab administration and are generally mild to moderate in severity. [redacted]

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

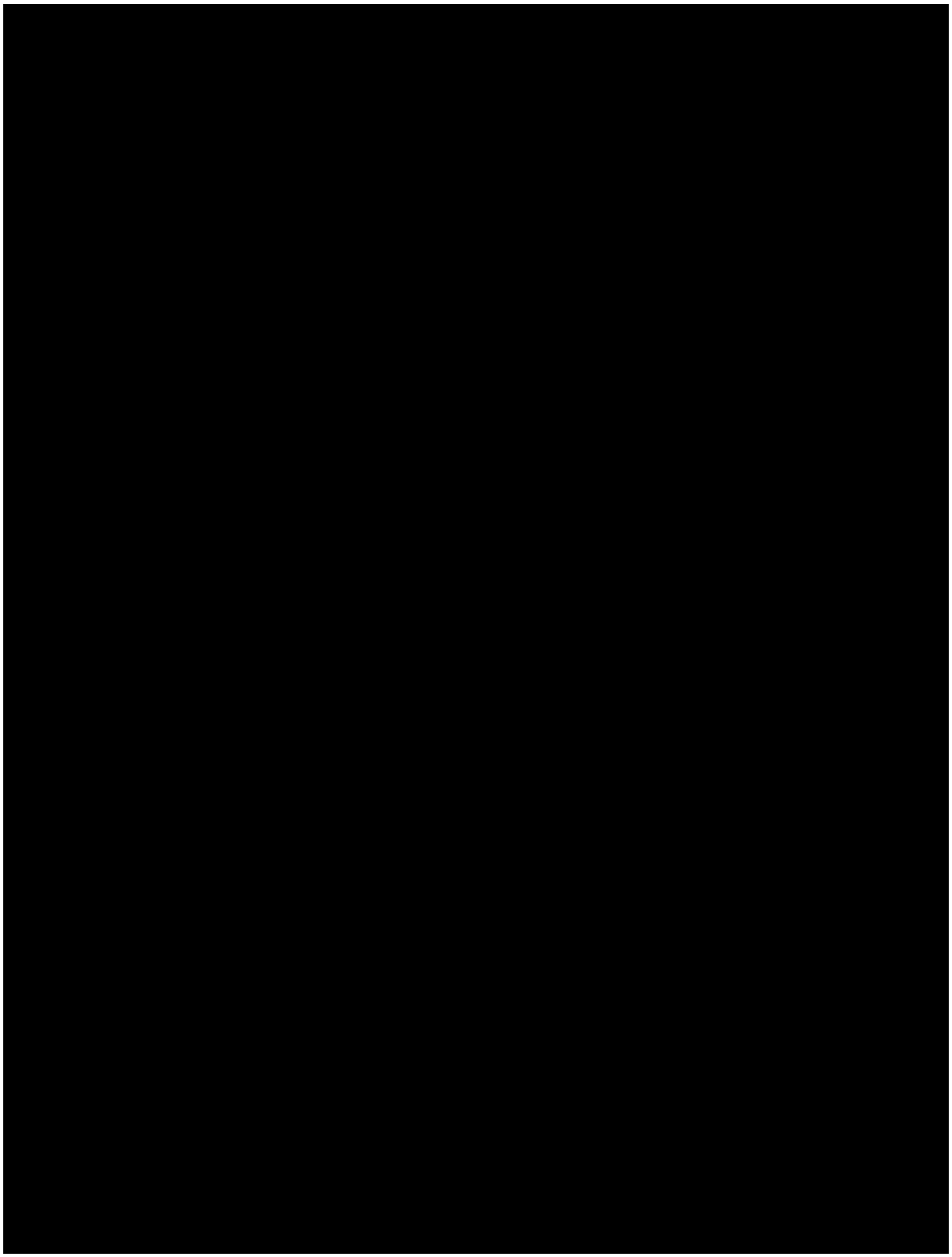
IRR = infusion-related reaction.

[redacted]

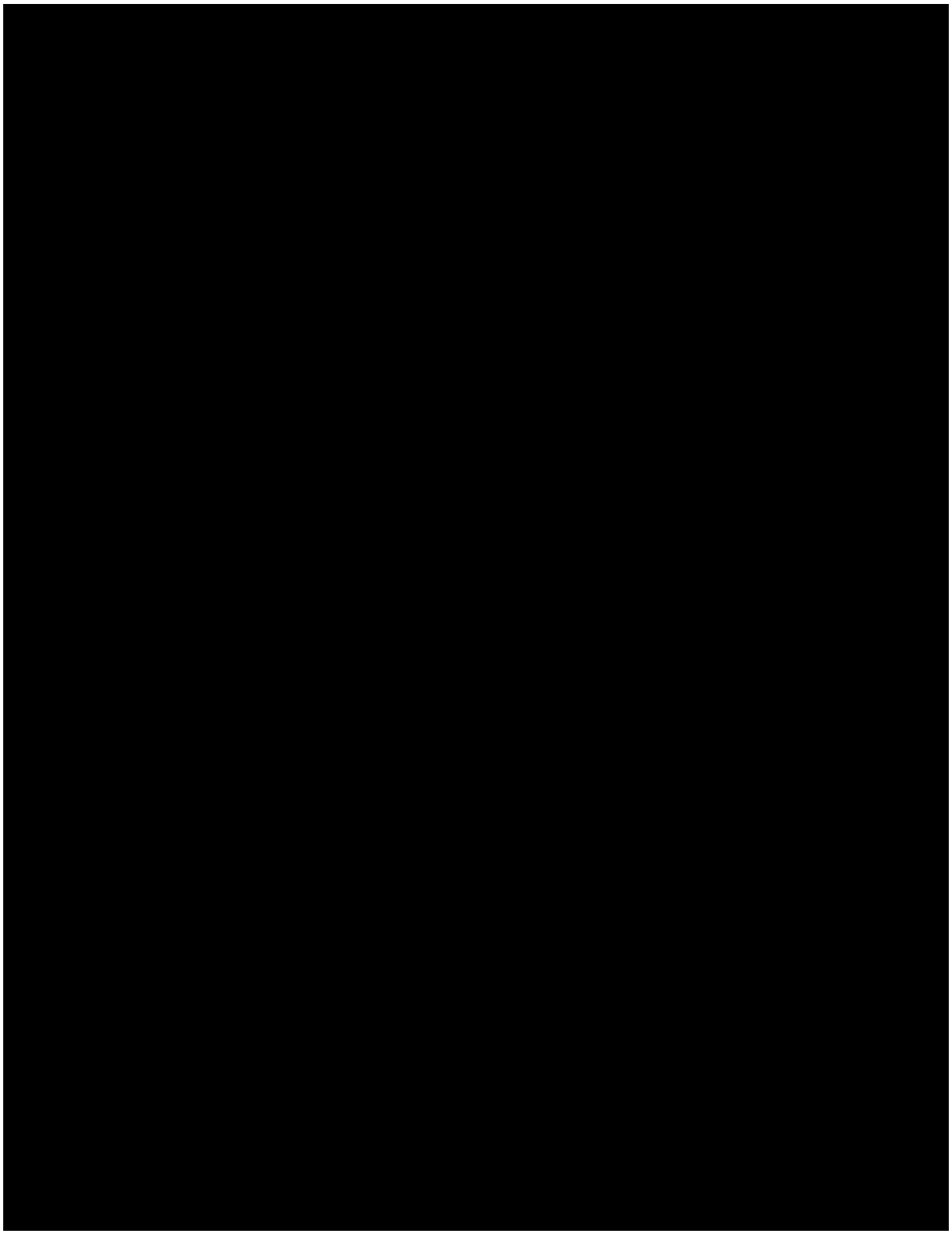
[redacted]

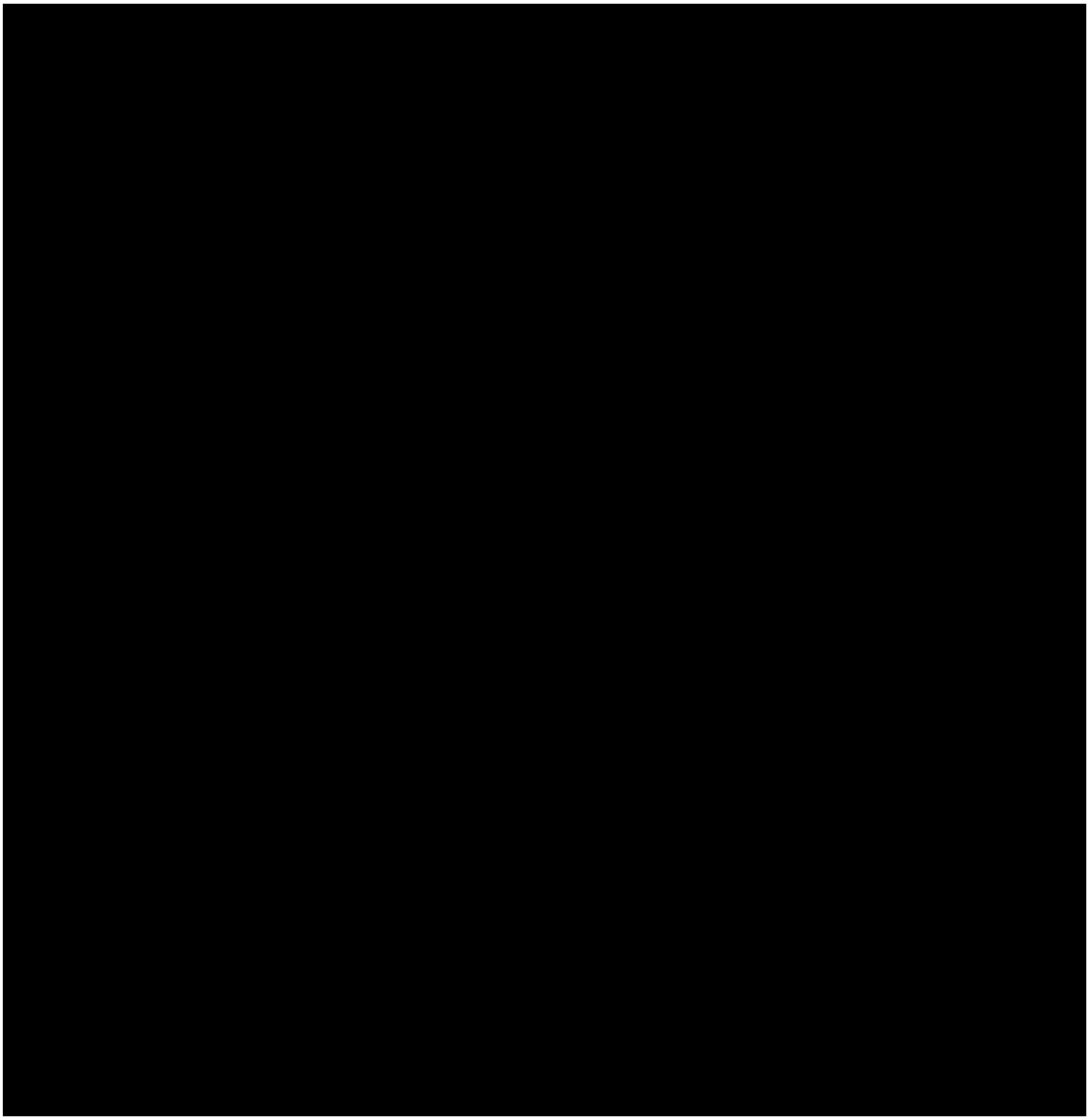
Appendix 12 Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

Appendix 12 Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab



Appendix 12 Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab





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 9.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	[redacted]
[redacted]	

GI = gastrointestinal.

[redacted]

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

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

[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]

Table 10 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

a [redacted]

b

c

Table 10 Management Guidelines for Dermatologic Events (cont.)

[redacted]

a [redacted]

b

c

NEUROLOGIC DISORDERS

Patients 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 in Table 11, with specific guidelines for myelitis provided in Table 12.

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
[redacted]	[redacted]

Table 11 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

Table 12 Management Guidelines for Immune-Mediated Myelitis

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient 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]

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	• [redacted]

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Renal Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

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. [redacted]

Appendix 12 Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

IVIG = intravenous immunoglobulin.

a [redacted]

b

c

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	[redacted]

Appendix 12 Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

[redacted]

- [redacted]

[redacted]

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Appendix 13
Investigational Non-Investigational, and Auxiliary Medicinal Product Designations (for Use in European Economic Area)

Table 1 Investigational, Authorized Auxiliary 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)	Authorized	No
Gemcitabine	AxMP (background treatment)	Authorized	Not applicable[a]
Paclitaxel	AxMP (background treatment)	Authorized	Not applicable[a]
Pemetrexed	AxMP (background treatment)	Authorized	Not applicable[a]
Carboplatin	AxMP (background treatment)	Authorized	Not applicable[a]
Cisplatin	AxMP (background treatment)	Authorized	Not applicable[a]

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

[a] The chemotherapies being provided to patients are SOC and listed in treatment guidelines, no study objectives related to gaining information on background treatment, there is no comparison between the cohorts, and the cohorts have different populations differentiated by PDL1 status.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Gemcitabine	Non-Roche NIMP (background treatment)	Authorized	Not applicable[a]
Paclitaxel	Non-Roche NIMP (background treatment)	Authorized	Not applicable[a]
Pemetrexed	Non-Roche NIMP (background treatment)	Authorized	Not applicable[a]
Carboplatin	Non-Roche NIMP (background treatment)	Authorized	Not applicable[a]
Cisplatin	Non-Roche NIMP (background treatment)	Authorized	Not applicable[a]

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

[a] The chemotherapies being provided to patients are SOC and listed in treatment guidelines, no study objectives related to gaining information on background treatment, there is no comparison between the cohorts, and the cohorts have different populations differentiated by PDL1 status.

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