Official Title:	A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck (Morpheus-Head and Neck Cancer)
NCT Number:	NCT05459129
Document Date:	Protocol Amendment Version 3: 29-January-2024

PROTOCOL

PROTOCOL **TITLE:**	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (MORPHEUS-HEAD AND NECK CANCER)**
PROTOCOL NUMBER:	CO43613
VERSION NUMBER:	3
TEST COMPOUNDS:	Atezolizumab (RO5541267), Tiragolumab (RO7092284), Paclitaxel, and Carboplatin
STUDY PHASE	Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 159031 EudraCT: 2021-005712-62 EU CT No: 2022-502733-26-00 Performance Study Identification Number (PS ID): *Not applicable* NCT Number: *NCT05459129*
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on final page of this document.
2	15 December 2022
1	21 January 2022

PROTOCOL AMENDMENT, VERSION 3
RATIONALE

Protocol CO43613 has been amended primarily to align with Atezolizumab Investigator's Brochure, Version 20. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- Events defining event-free survival have been clarified for secondary efficacy objectives (Section 2, Table 2).
- It has been clarified that surgery period can be scheduled until [redacted] with actual surgery deviating from the planned date by [redacted] (Sections 3.1.2 and 3.1.4).
- Text has been revised to clarify eligibility criteria for histologically confirmed, resectable Stage III–IV squamous cell carcinoma of the head and neck (Section 4.1.1).
- Text on local programmed death–ligand 1 results [redacted]
- Text have been revised to clarify eligibility criteria for Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb) and Hepatitis B core antibody (HBcAb) tests at screening. [redacted]
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 4.1.2).
- It has been specified that weight will be reported at screening (Section 4.5.3).
- Text has been added to reference vital signs details for study treatment (Section 4.5.4).
- Text has been revised to clarify that 12-lead ECG will be performed at screening, as outlined in the schedule of activities and as clinically indicated (Section 4.5.5).
- Text has been added to clarify that MRI scans with contrast of pelvis must be performed as applicable and/or per clinical standard (Section 4.5.6.1).
- Text has been added to clarify that at the treatment completion or discontinuation visit between [redacted], disease status will be assessed by radiographic tumor assessments for the absence of recurrent disease and should include a CT scan or MRI (Section 4.5.6.2, and footnote 'f' in Appendices 9 [Section A9-6] and 11 [Section A11-6]).
- Text has been revised to clarify that tumor tissue containing bone and decalcified tissue are not acceptable (Section 4.5.11.2).

- Text has been added to specify that the Sponsor may decide to close a specific arms if approximately 80% of patients discontinue from the study or all patients have been followed up for at least 2 years, whichever occurs first (Section 4.6.1, and footnote 'c' in Appendices 9 [Section A9-6] and 11 [Section A11-6]).
- Text has been added to specify that after the end of the reporting period for non-serious adverse events all treatment-related non-serious adverse events that lead to surgery delay will continue to be reported until [redacted] days after the final dose of study treatment (Section 5.6, and footnote 'g' in Appendices 9 [Section A9-6] and 11 [Section A11-6]).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- Text has been added to clarify that patients with missing or no pathological response evaluation will be classified as non-pathological responders (Section 6.4.1).
- Duplicate text regarding verbatim adverse event terms and grading of adverse event severity have been removed (Section 6.5).
- Serum autoantibodies assessment has been removed as serum samples will not be collected for autoantibodies at screening (Appendix 6).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendices 7 [Tables A7-1, A7-3, A7-4, A7-6, A7-7, A7-9 to 11, and A7-13 to 15] and 11 [Section A11-5.3; Table A11-7]).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Appendices 9 [Section A9-1.1] and 11 [Section A11-1]).
- Footnote 'a' has been extended to all visits to allow that visit can occur outside a specific window if precluded because of a holiday, vacation, or other circumstance (Appendices 9 [Section A9-6] and 11 [Section A11-6]).
- Text has been added to specify that [redacted] at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment (footnote 'j' in Appendices 9 [Section A9-6] and 11 [Section A11-6]).
- Text has been added to specify +2 days time window for Day 1 of Cycle 2 (Appendices 9 [Section A9-6] and 11 [Section A11-6]).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

***PROTOCOL* TITLE:**	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (MORPHEUS-HEAD AND NECK CANCER)**
PROTOCOL NUMBER:	CO43613
VERSION NUMBER:	3
TEST PRODUCTS:	Atezolizumab (RO5541267), Tiragolumab (RO7092284), Paclitaxel, and Carboplatin
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local monitor.

PROTOCOL SYNOPSIS

PROTOCOL **TITLE:**	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (MORPHEUS-HEAD AND NECK CANCER)**
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 159031 EudraCT: 2021-005712-62 EU CT No: 2022-502733-26-00 Performance Study Identification Number (PS ID): *Not applicable* NCT Number: *NCT05459129*

STUDY RATIONALE

This study will evaluate the efficacy, safety, and pharmacokinetics of treatment combinations in treatment-naive patients with locally advanced Stage III–IVA resectable squamous cell carcinoma of the head and neck (SCCHN). Locally advanced (Stage III–IVB) SCCHN is associated with a high risk for both local recurrence and distant metastases and is treated with definitive local therapy. Neoadjuvant checkpoint inhibition has been demonstrated to be safe and to not affect the timely conduct of surgery in locally advanced SCCHN patients.
The combination of immune checkpoint inhibition with agents or techniques targeting different immune-evasion mechanisms may further increase response rates and decrease the rate of disease recurrence in this population.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• pCR, defined as the absence of any viable primary tumor at time of surgical resection, as determined by local pathologic review
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• pRR as determined by local pathologic review. pRR is defined as the proportion of participants with pCR, mPR (≤10% residual viable tumor at the time of surgical resection in the primary tumor), and pPR (≤50% residual viable tumor at the time of surgical resection in the primary tumor) • EFS, defined as the time from randomization to any of the following events (whichever occurs first): – disease progression that precludes surgery, as determined by the investigator according to RECIST v1.1 – local, regional, or distant disease recurrence – death from any cause • RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause • OS, defined as the time from randomization to death from any cause • ORR, defined as the proportion of patients with a complete response or a partial response, as determined by the investigator according to RECIST v1.1, prior to surgery Responses will be assessed and determined according to RECIST v1.1 but are not required to be confirmed by subsequent imaging studies. • *Landmark EFS, defined as the time from randomization to any of the following events (whichever occurs first):* – *disease progression that precludes surgery, as determined by the investigator according to RECIST v1.1* – *local, regional, or distant disease recurrence* – *death from any cause at specified timepoints (1, 2, 3, and 5 years)* • *Landmark RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause at specified timepoints (1, 2, 3, and 5 years)* • *Landmark OS, defined as the time from randomization to death from any cause at specified timepoints (1, 2, 3, and 5 years)*

Safety Objective	Corresponding Endpoints
• To evaluate the safety of treatment	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 • Incidence and nature of Grade ≥3 immune-related adverse events during the first 12 weeks • Rate and duration of delayed surgery due to treatment-related adverse events • Rate of surgical complications, as assessed according to the Clavien-Dindo surgical classification

ADA=anti-drug antibody; EFS=event-free survival; ORR=objective response rate; OS=overall survival; pCR=pathologic complete response; PK=pharmacokinetic; mPR=major pathologic response; pPR=partial pathologic response; pRR=pathologic response rate; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS=relapse-free survival.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with locally advanced SCCHN. The study will enroll treatment-naive patients with resectable Stage III–IVA human papillomavirus (HPV)-negative, programmed death–ligand 1 (PD-L1)–positive SCCHN with measurable disease, as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) who have not received systemic treatment for their disease (e.g., PD-L1/PD-1– and/or cytotoxic T lymphocyte antigen–4–blocking agents or other agents).

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

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Squamous cell carcinoma of the head and neck
Interventional Model:	Parallel group	**Population Age:**	≥18 years
Test Compounds:	Atezolizumab (RO5541267), Tiragolumab (RO7092284), Paclitaxel, and Carboplatin	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 12–90 patients

STUDY TREATMENT

Study Treatment	
Treatment Group	Administration Method and Schedule
Atezolizumab plus tiragolumab (CIT combination treatment) (21-day cycles)	• Atezolizumab: IV infusion over 30–60 minutes on Day 1 of each cycle. • Tiragolumab: IV infusion over [redacted] minutes on Day 1 of each cycle
Atezolizumab in combination with tiragolumab and chemotherapy [a] (CIT combination plus chemotherapy [a]) (21-day cycles)	• Atezolizumab: IV infusion over 30–60 minutes on Day 1 of each cycle. • Tiragolumab: IV infusion over [redacted] minutes on Day 1 of each cycle. • Chemotherapy [a]: IV infusion over *210–240* minutes on Day 1 of each cycle.

CIT = cancer immunotherapy; IV = intravenous.

[a] chemotherapy will be a combination of carboplatin and paclitaxel.

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

For management of drug-related toxicities, the dose of paclitaxel and dose of carboplatin may be reduced by up to two times, as outlined in *Table 1*.

Table 1 Dose Reductions for Paclitaxel and Carboplatin

	Initial and approved Dose	Reduced by One Dose Level	Reduced by Two Dose Levels
Paclitaxel	175 mg/m^2	135 mg/m^2	90 mg/m^2
Carboplatin	AUC 5	AUC 3.75	AUC 2.5

AUC = area under the concentration–time curve.

DURATION OF PARTICIPATION

The total duration of study participation for each individual from screening until treatment completion visit and start of adjuvant treatment is expected to be approximately 17 weeks (not including follow up) and includes:

- Screening: Days –28 to –1
- Treatment period: 13 weeks; participants will receive neoadjuvant treatment during a 6-week period and will undergo surgery [redacted]. After surgery and prior to commencing adjuvant treatment, treatment completion will be performed [redacted]

Participants may continue on the study, including the following visits:

- During the follow-up period, disease status should be clinically evaluated and documented approximately every 3 months (according to local or institutional guidelines and standards) for the first 2 years; every 6 months during Years 3, 4, and 5; and once a year during Year 6 and subsequent years
- Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee, Scientific Oversight Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
[redacted]	
Atezo	atezolizumab
C	carboplatin
CI	confidence interval
CIT	cancer immunotherapy
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CPS	combined positive score
CRS	cytokine release syndrome
CRT	chemoradiotherapy
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte antigen–4
DOR	duration of response
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
5-FU	5-fluorouracil
FDA	(U.S.) Food and Drug Administration
[redacted]	
FU	fluorouracil
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen

Abbreviation	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papillomavirus
HR	hazard ratio
I	ipilimumab
IFN-γ	interferon-γ
IHC	immunohistochemistry
IL-2 (-6, -10)	interleukin-2 (-6, -10)
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive web-based response system
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
mPR	major pathologic response
MRI	magnetic resonance imaging
N	nivolumab
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
OS	overall survival
OCSCC	oral cavity squamous cell carcinoma
P	paclitaxel
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	pathologic response

Abbreviation	Definition
pRR	pathologic response rate
Q3W	every 3 weeks
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RFS	relapse-free survival
RT	radiotherapy
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SITC	Society for Immunotherapy of Cancer
SOC	*standard-of-care*
T3	triiodthyroninine
T4	thyroxine
TIGIT	T-cell immunoreceptor with immunoglobulin and ITIM domains
Tira	tiragolumab
TNF-α	tumor necrosis factor–α
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Head and neck cancer is a cause of significant morbidity and mortality, accounting for 890,000 new cases and 450,000 deaths globally in 2018 (Bray et al. 2018). Head and neck cancer is a heterogeneous group, comprising cancers that begin in the mucosal surfaces of the upper aerodigestive tract and affect the oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx. The dominant histological type is squamous cell carcinoma, which accounts for more than 90% of all malignant disease in the head and neck region of the body. The risk factors for squamous cell carcinoma of the head and neck (SCCHN) disease include tobacco use, alcohol consumption, and infection with human papillomavirus (HPV) (Sankaranarayanan et al. 1998; Wyss et al. 2013; Vokes et al. 2015).

Historically, SCCHN has been a disease for older males with heavy lifelong tobacco use, high alcohol consumption, poor diet, and bad dentition. The effects of tobacco and alcohol, when used alone or in combination, have been shown to increase the risk for head and neck cancers (Blot et al. 1988). Long-term smoking and alcohol use are also contributing factors in the development of second primary tumors in the head and neck region, esophagus, and lungs in patients with SCCHN, owing to the field cancerization effect (Slaughter et al. 1953; Erkal et al. 2001). However, more patients are now being diagnosed with oropharyngeal cancers in their 40s (Shiboski et al. 2005), and HPV infection, especially HPV-16, has been associated with the development of these types of cancers (Gillison et al. 2000; Mendenhall and Logan 2009). Although patients with HPV-positive SCCHN tend to be younger and are less likely to have a history of significant smoking and alcohol use, they have a history of multiple sexual partners and orogenital sexual activity. HPV-associated SCCHN tumors tend to have a better prognosis and a lower rate of second primary tumors (Ang et al. 2010). Patients with head and neck cancer report significant and persistent physical (i.e., mucositis, loss of taste, and dysphagia), functional (i.e., pain, difficulty swallowing, voice impairment, and poor dental status), and psychosocial problems (Ojo et al. 2012).

Approximately one-third of newly diagnosed patients with SCCHN present with Stage I or II (early-stage) disease and are treated with either primary surgery or definitive radiotherapy (RT). The 5-year overall survival (OS) rate in patients with Stage I or II disease is between 70% and 90% (Brockstein et al. 2020). RT and surgery are equally effective treatments, with the choice of therapy dependent on the anatomic site, surgical expertise, accessibility of the tumor, and the functional outcomes and morbidity associated with each modality.

The majority of patients with SCCHN present with locally advanced disease (Stage III–IVB). Although such patients are treated with definitive local therapy, locally advanced disease is associated with poor outcomes, with a median OS of approximately

20 months (Adelstein et al. 2003). Patients who are HPV negative with Stage IVA and IVB SCCHN have a 5-year OS rate of <25% (Denis et al. 2004), and patients who are HPV positive with Stage III disease have a 5-year survival rate of 50% (Vokes et al. 2015; O'Sullivan et al. 2016).

Despite advances in diagnosis and treatment of early-stage or locally advanced SCCHN, more than 65% of patients will develop recurrent or metastatic disease (Argiris et al. 2011; Chow 2020). In addition, approximately 10% of patients with SCCHN will present with metastatic SCCHN at initial diagnosis (Ridge et al. 2011). For patients with locally recurrent disease, salvage surgery is curative only for selected patients with resectable locoregional recurrence, and re-irradiation is often limited by history of RT and associated toxicity and morbidity (Argiris et al. 2011; Chow 2020). As a result, for patients with recurrent or metastatic (HPV-negative Stage IVC and HPV-positive Stage IV disease) SCCHN, systemic therapy is a standard-of-care (SOC) treatment and is a mainstay of palliation. Prognosis in this clinical setting is poor, with a median survival of 6–12 months in most clinical trials, depending on patient- and disease-related factors. Combination chemotherapy with cisplatin or carboplatin and 5-fluorouracil (5-FU), with or without cetuximab, is usually the first-line treatment option for fit patients (Clavel et al. 1994; Forastiere et al. 1998; Gibson et al. 2005; Vermorken et al. 2008).

Recently, pembrolizumab was approved for in combination with platinum and fluorouracil (5-FU) for the treatment of patients with metastatic SCCHN regardless of tumor programmed death–ligand 1 (PD-L1) expression and as a single-agent treatment for patients whose tumors express PD-L1 (combined positive score [CPS] ≥ 1), as determined using a U.S. Food and Drug Administration (FDA)-approved test. Approval was based on the KEYNOTE-048 (NCT02358031) study (Burtness et al. 2019), a randomized, three-arm, open-label, active-controlled, multicenter trial conducted in 882 patients with metastatic SCCHN who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies.

In the second-line and beyond treatment settings, single agents are commonly used, and pembrolizumab (Chow et al. 2016; Larkins et al. 2017) and nivolumab (Ferris et al. 2016) have been approved.

1.1.1 Treatment of SCCHN

Checkpoint inhibitor (CPI) therapies have shown activity in metastatic SCCHN in the first- , second- , and third-line settings and beyond (Chow et al. 2016; Ferris et al. 2016; Burtness et al. 2019). Both nivolumab and pembrolizumab, which target programmed death–1 (PD-1), have been approved by the U.S. FDA for the treatment of patients who have previously been treated for recurrent or metastatic SCCHN (Opdivo® U.S. Package Insert; Keytruda® U.S. Package Insert). Nivolumab is also approved in the European Union for the treatment of SCCHN in adults progressing during or after platinum-based therapy (Opdivo Summary of Product Characteristics).

In the KEYNOTE-012 (Seiwert et al. 2016) and KEYNOTE-055 (Bauml et al. 2017) studies of pembrolizumab, patients with recurrent or metastatic SCCHN or platinum- and cetuximab-refractory SCCHN, respectively, had an objective response rate (ORR) of 16%–18%. The response rate was 25% in HPV-positive patients (reported for 4 of 16 patients (95% confidence interval [CI]: 7% to 52%) and 14% in HPV-negative patients (4 of 29 patients; 95% CI: 4% to 32%); all patients were PD-L1 positive. Recently, results from the Phase III, randomized KEYNOTE-048 (NCT02358031) study led to the approval of pembrolizumab in combination with platinum and fluorouracil for the treatment of patients with metastatic SCCHN regardless of tumor PD-L1 expression and as a single-agent treatment of patients whose tumors express PD-L1 (CPS ≥1), as determined by a U.S. FDA-approved test (for details, please see Section 1.1).

A Phase III trial (CheckMate 141) (Ferris et al. 2016) demonstrated that patients who have platinum-refractory, recurrent, or metastatic SCCHN treated with nivolumab had a longer OS (median: 7.5 vs. 5.1 months; hazard ratio [HR]: 0.70; 97.7% confidence interval [CI}: 0.51 to 0.96) and increased ORR (13.3% vs. 5.8%) relative to patients treated with single-agent investigator's choice of therapy. An updated analysis of the study (minimum follow-up: 11.4 months) demonstrated similar results: longer OS (median: 7.7 vs. 5.1 months; HR: 0.71; 95% CI: 0.55 to 0.90) and increased ORR (13.3% vs. 5.8%) (Gillison et al. 2018).

Atezolizumab has also shown encouraging activity in metastatic and recurrent SCCHN in Study PCD4989g (see Section 3.4.2). Based on results of these clinical studies, blockade of the PD-L1/PD-1 pathways with atezolizumab, pembrolizumab, or nivolumab has demonstrated efficacy in patients with SCCHN.

1.1.1.1 First-Line Chemotherapy for Recurrent and Metastatic SCCHN

Platinum-based systemic chemotherapy has been considered the SOC for the first-line treatment of recurrent and metastatic SCCHN for decades. The Phase III EXTREME trial established the combination of cetuximab with 5-FU and platinum chemotherapy (cisplatin or carboplatin) as the SOC treatment for recurrent and metastatic SCCHN in the first-line setting based on improvements of 10.1 months in OS compared with 7.4 months (HR: 0.80; 95% CI: 0.64 to 0.99; p=0.04) and progression-free survival (PFS) of 5.6 months compared with 3.3 months (HR: 0.54) compared with 5-FU and platinum chemotherapy (Vermorken et al. 2008). Despite survival improvements, outcomes are still poor, and this regimen is associated with substantial toxicity and is generally poorly tolerated by elderly patients and patients with poor performance status and comorbidities.

1.1.1.2 First-Line Immunotherapy for Recurrent and Metastatic SCCHN

SCCHN has generally been associated with deficiencies in the immune system. A high mutational rate is associated with SCCHN that may contribute to increased immunogenicity, potentially making the disease responsive to immunotherapy (Lawrence et al. 2013). SCCHN has been shown to evade host cellular immune response by

means of upregulation of T cell–suppressive ligands, including PD-L1, which leads to inhibition of T-cell function and tumor evasion (Ferris et al. 2015). Nonclinical data suggest that PD-L1 expression is high in the oropharyngeal area (Lyford-Pike et al. 2013) and patients with HPV-positive and HPV-negative SCCHN have been shown to express PD-L1 (Badoual et al. 2013; Concha-Benavente et al. 2016).

1.1.1.3 CPI Therapy and Chemotherapy for First-Line Treatment of Recurrent and Metastatic SCCHN

The KEYNOTE-048 trial demonstrated a statistically significant improvement in the primary endpoint of OS in patients with a PD-L1 CPS ≥1 and in the overall population of patients who were treated with pembrolizumab and chemotherapy compared with patients who were treated with cetuximab and chemotherapy. In the CPS ≥1 population, median OS was 13.6 months in the pembrolizumab and chemotherapy arm relative to 10.4 months in the cetuximab and chemotherapy arm (HR: 0.65; 95% CI: 0.53 to 0.80; $p<0.0001$). In the overall population, median OS was 13 months in the pembrolizumab and chemotherapy arm compared with 10.7 months in the cetuximab and chemotherapy arm (HR: 0.77; 95% CI: 0.63 to 0.93; $p=0.0034$) (Burtness et al. 2019).

There was no statistically significant improvement in PFS observed with pembrolizumab and chemotherapy compared with cetuximab and chemotherapy in both PD-L1 populations (CPS ≥1 [HR: 0.82; 95% CI: 0.67 to 1.00]) and in the overall population (HR: 0.92; 95% CI: 0.77 to 1.10; $p=0.1697$). Response rates were similar for pembrolizumab and chemotherapy compared with cetuximab and chemotherapy in all PD-L1 populations, although the median duration of response (DOR) for pembrolizumab and chemotherapy was numerically longer in the overall patient population. Patients with a CPS ≥1 demonstrated a DOR of 6.7 months relative to 4.3 months, and the overall population demonstrated a DOR of 6.7 months compared with 4.3 months.

Pembrolizumab in combination with platinum-based and 5-FU chemotherapy was approved by the U.S. FDA for the treatment of patients with metastatic or unresectable, recurrent SCCHN regardless of PD-L1 status and by the European Medicines Agency (EMA) for patients whose tumors express PD-L1 with a CPS ≥1 (Keytruda® U.S. Package Insert; Keytruda® Summary of Product Characteristics).

1.1.1.4 CPIs as Monotherapy for First-Line Treatment of Recurrent and Metastatic SCCHN

In the KEYNOTE-048 trial, a statistically significant improvement in OS was demonstrated with pembrolizumab monotherapy compared with cetuximab and chemotherapy in the patient populations with a PD-L1 CPS ≥20 and CPS ≥1. In patients with a CPS ≥20, an OS benefit was observed with pembrolizumab monotherapy relative to that with cetuximab and chemotherapy, with a median OS of 14.9 months relative to 10.7 months, respectively (HR: 0.61; 95% CI: 0.45 to 0.83; $p=0.0007$) (Burtness et al. 2019).

In patients with a CPS ≥1, median OS was 12.3 months with pembrolizumab monotherapy compared with 10.3 months with cetuximab and chemotherapy (HR: 0.78; 95% CI: 0.64 to 0.96; p=0.0086). There was no statistically significant improvement in OS demonstrated in the overall population, with a median OS of 11.6 months compared with 10.7 months (HR: 0.85; 95% CI: 0.71 to 1.03).

In comparison, there was no improvement in PFS observed with pembrolizumab monotherapy between cetuximab and chemotherapy and PD-L1 populations with a CPS ≥20 (HR: 0.99; 95% CI: 0.75 to 1.29; p=0.4562) and a CPS ≥1 (HR: 1.16; 95% CI: 0.96 to 1.39). The response rate was lower with pembrolizumab monotherapy compared with cetuximab and chemotherapy in both PD-L1 populations. Patients with a CPS ≥20 demonstrated a response rate of 23% relative to 36%, and patients with a CPS ≥1 demonstrated a response rate of 19% compared with 35%. However, responses were more durable with pembrolizumab monotherapy relative to those with cetuximab and chemotherapy, as demonstrated by the longer median DOR of 22.6 months compared with 4.2 months in patients with a CPS ≥20 who were treated with pembrolizumab and patients with a CPS ≥1 with a median DOR of 23.4 months compared with 4.5 months (Burtness et al. 2019).

Based on these data, pembrolizumab as monotherapy was approved by the U.S. FDA and the EMA for the first-line treatment of patients with metastatic or unresectable, recurrent SCCHN whose tumors express PD-L1 with a CPS ≥1 (Keytruda® U.S. Package Insert; Keytruda® Summary of Product Characteristics).

In addition, several studies have demonstrated the clinical activity of PD-L1 CPI agents in SCCHN:

A total of 32 efficacy-evaluable patients with SCCHN have been enrolled in the Phase I study PCD4989g, assessing safety and efficacy of atezolizumab as a monotherapy. Of the 32 patients, 84% of patients were male, 66% had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 1, and 34% had an ECOG Performance Status of 0. The median age of patients was 62 years (range: 32–78 years). Patients had been heavily pretreated (53% of patients had received two or more prior lines of therapy). Primary tumor sites included the oropharynx (56% of patients), oral cavity (22%), nasopharynx (13%), larynx (6%), and hypopharynx (3%). Of the 28 patients with non-nasopharyngeal cancer, 46% of patients tested positive for human papillomavirus (HPV), 43% tested negative for HPV, and 11% had HPV of unknown status (Colevas et al. 2018).

The confirmed ORR in the 32 enrolled patients was 22% (95% CI: 9.3% to 40.0%), and DOR was 7.4 months (95% CI: 2.8 to 45.8 months). Median PFS was 2.6 months (range: 0.5–48.4 months), and median OS was 6.0 months (range: 0.5–51.6 months to censored value) (Colevas et al. 2018).

In a Phase I/II study, assessing the safety and efficacy of durvalumab in heavily pretreated patients with SCCHN, 62 patients were enrolled (Segal et al. 2019). Of the 62 patients, 40.3% were HPV positive and 32.3% had tumor cell PD-L1 expression ≥25%. Patients had received a median of two prior systemic treatments. All-causality adverse events were reported in 98.4% of patients; study drug–related adverse events were reported in 59.7% of patients and were of Grade III or IV severity in 9.7%. No study drug–related discontinuations or deaths were reported. The ORR was 6.5% (15.0% of patients with PD-L1 tumor cell expression ≥25%, 2.6% of patients with PD-L1 expression <25%). Median time to response was 2.7 months (range: 1.2–5.5 months), with a median DOR of 12.4 months (range: 3.5–20.5 months). Median PFS was 1.4 months, and median OS was 8.4 months. The OS rate was 62% at 6 months and 38% at 12 months (42% patients with PD-L1 tumor cell expression ≥25%, and 36% of patients with PD-L1 expression <25%) (Segal et al. 2019).

1.1.2 Treatment for Locally Advanced SCCHN

Locally advanced (Stage III–IVB) SCCHN is associated with a high risk for both local recurrence and distant metastases and is treated with definitive local therapy. Definitive local therapy consists of combined modality approaches to optimize the chances for long-term disease control. Such combined modality approaches include primary surgery followed by either postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy based on taxane and platinum combinations followed by primary surgery and/or RT or CRT, induction chemotherapy based on taxane and platinum combinations followed by RT or CRT alone, concurrent CRT without surgery, or CRT followed by salvage surgery. A number of factors affect the choice of definitive local therapy (primary surgery vs. CRT vs. combination of surgery plus CRT), including patient age, performance status, preexisting co-morbidities, and the anatomical site of the tumor.

Patients with resectable disease are treated with a combination of surgery, RT, and chemotherapy, either as definitive combined chemotherapy and radiation or surgical extirpation, followed by adjuvant radiation, with or without chemotherapy.

In the latter approach, postoperative adjuvant treatment is guided by pathologic findings for which patients receive either radiation alone or more intensive combined chemotherapy and radiation based on their postoperative risk status.

Studies have shown that combining chemotherapy with RT postoperatively reduces the risk of recurrence of disease compared with patients who receive RT alone (Bernier et al. 2004; Cooper et al. 2004). In addition to postoperative concurrent treatment with cisplatin and RT, concurrent treatment with cetuximab and RT has also been shown to confer a benefit in locoregional control and survival compared with RT alone (Bonner et al. 2006).

Despite the addition of these modalities, a "high-risk" subgroup of patients (patients with positive margins or lymph node extracapsular extension) treated with radiation and chemotherapy suffer disease-specific mortality and may benefit most from novel therapeutic intensification approaches.

The current SOC for patients with locally advanced SCCHN who are not surgical candidates includes a combination of RT (65–70 Gy in 35 fractions administered over 7 weeks) with concurrent cisplatin treatment (most commonly given 100 mg/m^2 every 3 weeks [Q3W] or less commonly 40 mg/m^2 once a day [QD] for the duration of RT) or concurrent treatment with cetuximab and RT QD (Bonner et al. 2006; Pignon et al. 2009).

1.1.2.1 Immunotherapy for Locally Advanced SCCHN

To date, six clinical trials of neoadjuvant PD-L1/PD-1 checkpoint blockade in newly diagnosed patients with resectable SCCHN have demonstrated promising clinical activity. The majority of patients had local regionally advanced disease (T >2 or node positive).

In the first trial, a single preoperative dose of a PD-1 CPI (e.g., pembrolizumab) was administered to 36 patients with resectable cancer (Uppaluri et al. 2020). Of the 36 patients, 44% of patients had a pathological treatment effect, defined as tumor necrosis, keratinous debris, and giant cellor histocytic reaction in >10% of the tumor specimen. Of the 36 patients, 2 patients (5.5%) had a classical major pathologic response (mPR; <10% viable tumor). The 1-year PFS rate of 16.7% in patients with a pathological treatment effect was considered favorable relative to historical controls given patients' advanced stage of disease. Several measures of baseline tumor immune infiltration were associated with a pathological treatment effect. Notably, T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and PD-L1 expression, as measured by RNA sequencing, increased in patients without a pathological treatment effect but not in patients with a treatment effect, suggesting these checkpoint agents inhibit responses.

In the second trial, 29 patients with oral cavity squamous cell carcinoma (OCSCC) were randomized to receive two doses of a PD-1 checkpoint blockade agent (nivolumab [N], n=14), with or without a cytotoxic T lymphocyte antigen–4 (CTLA-4) blockade agent (ipilimumab [I]; [N+I]; n=5). Responses, assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), were observed in 13% (N) and 38% (N+I) *of patients*, and pathologic completes responses (pCRs) were observed in 8% (N) and 20% (N+I) of patients, respectively (Schoenfeld et al. 2020). Grade 3 and 4 toxicities attributable to systemic therapy were observed in 2 patients in the N monotherapy arm and 4 patients in the N+I arm. No delays in surgery or increase in surgical complications were noted (Schoenfeld et al. 2020).

In the third study presented at the 2021 annual meeting of the American Society of Clinical Oncology (ASCO), 92 patients with resectable, local regionally advanced cancer who were unselected on the basis of PD-L1 CPS received a single dose of neoadjuvant pembrolizumab prior to surgical resection (Wise-Draper et al. 2021). Of the 80 patients evaluable for pathologic response (PR), 32 patients had a PR, defined as tumor necrosis and/or histiocytic inflammation and giant cell reaction to keratinaceous debris in more than 20% of tumor. In a previous presentation of this study (Wise-Draper et al. 2020), patients with a PR and high- or intermediate-risk features who received adjuvant pembrolizumab, RT, with or without cisplatin, had significantly greater 1-year disease-free survival (DFS) than patients without a PR (100% vs. 57%; $p=0.0033$; HR: 0.18; 95% CI: 0.05 to 0.64) (Wise-Draper et al. 2021).

The fourth study was conducted by Zinner et al. (2020) and presented at the European Society of Medical Oncology (ESMO) in 2020. The study enrolled 32 patients with locally advanced Stage III and IV HPV-negative and Stage II and III HPV-positive oropharyngeal cancer and treated with a PD-1 inhibitor (240 mg IV nivolumab every 2 weeks $\times$ 3) in combination with paclitaxel (100 mg/m^2 IV once a week $\times$ 6) and carboplatin (area under the concentration–time curve [AUC] 2 QD $\times$ 6). Surgery was performed at Week 8. All 32 patients enrolled completed neoadjuvant therapy with the PD-1 inhibitor as well as both chemotherapy agents. Of the 32 patients, 37% of patients experienced presurgical Grade 3 and 4 adverse events (regardless of relationship to study treatment), including febrile neutropenia (10%), diarrhea (3%), cellulitis (3%), and rash (3%). The dose of chemotherapy was reduced in 7% of patients. All patients underwent surgery without delay. In the subset of HPV-negative patients, 42% of evaluable patients achieved a pCR at the primary tumor site.

In the Checkmate-358 study published by Ferris et al. (2021), 52 patients with Stage III and IV resectable SCCHN (assessed according to the American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 7th edition) received neoadjuvant therapy with nivolumab. Twenty-six patients were HPV positive and 26 were HPV negative. Treatment-related adverse events of any grade were experienced by 19 patients (73.1%) and 14 patients (53.8%) in the HPV-positive and HPV-negative cohorts, respectively; Grade 3 and 4 treatment-related adverse events were reported in 5 patients (19.2%) and 3 patients (11.5%), respectively. Importantly, no patient had a protocol-defined treatment-related adverse event of surgical delay >4 weeks. Of the 52 patients, 38 patients underwent complete surgical resection. The radiographic response rate in 49 evaluable patients were 12.0% and 8.3% in the HPV-positive and HPV-negative cohorts, respectively. No complete pathologic responses (PRs), assessed by site or central review, were reported in operated patients. Of 17 patients with centrally evaluable HPV-positive tumors, 1 patient (5.9%) achieved a major pathological response (mPR) and 3 patients (17.6%) achieved a partial pathologic response (pPR). Of the 17 patients with centrally evaluable HPV-negative tumors, 1 patient (5.9%) achieved a pPR (Ferris et al. 2021).

These trials demonstrate that neoadjuvant checkpoint blockade is safe and feasible in the preoperative setting for patients with SCCHN. The data support further investigation of the clinical benefit of neoadjuvant immunotherapy combinations in newly diagnosed patients with locally advanced SCCHN.

An ongoing Phase III, randomized study (KEYNOTE-689 [NCTNCT03765918]) is comparing neoadjuvant treatment with two cycles of pembrolizumab followed by surgery and risk-adapted adjuvant therapy, with or without pembrolizumab, with no neoadjuvant therapy followed by surgery and risk-adapted SOC.

1.2 STUDY RATIONALE

This Phase Ib/II, randomized umbrella study is designed to accelerate the development of treatment combinations by identifying early signals and establishing proof-of-concept clinical data in patients with resectable SCCHN. The study will enroll patients with locally advanced, resectable Stage III–IVA PD-L1–positive, HPV-negative SCCHN tumors, assessed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition (Amin et al. 2017).

The currently prevailing cancer immunotherapy (CIT) approach is to circumvent immune-evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors such as PD-L1 and PD-1. Other approaches build on the removal or inhibition of tumor-promoting cell types or employ immune stimulation by means of cytokines, engagement of costimulatory receptors, or antibody-directed T-cell activation.

Single-agent immune CPIs, CPI and chemotherapy combinations, CPI-immune combinations, and CPIs in combination with targeted therapies have shown promising results in SCCHN and are approved for the treatment of patients with recurrent and/or metastatic SCCHN.

Furthermore, CIT has demonstrated clear clinical efficacy, with significant survival benefit observed across multiple advanced malignancies and there is evidence that PD-L1/PD-1 checkpoint blockade can generate mPRs and durable responses in patients with resectable SCCHN (Schoenfeld et al. 2020; Uppaluri et al. 2020; Wise-Draper et al. 2021), without delaying surgery. Although these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is necessary for the generation of an effective anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response is critical for propagating cancer immunity and advancing the field of CIT. The combination of PD-L1/PD-1 blocking with agents or techniques targeting different immune-evasion mechanisms may further increase response rates and decrease the rate of disease recurrence in this population.

The potential risks for patients will be adverse events associated with study treatments. Adverse events could potentially affect the timely conduct of surgery. Furthermore, the course of postsurgery recovery may be altered with neoadjuvant CIT. However, these theoretical concerns have not been borne out by data from recent studies in the neoadjuvant setting in SCCHN (e.g., Leidner et al. 2021) and in other indications such as melanoma (Blank et al. 2018; Rozeman et al. 2019).

In summary, studies in the neoadjuvant setting in patients with locally advanced, resectable SCCHN have demonstrated that neoadjuvant treatment does not affect the timely conduct of surgery or result in a significant increase in operative or postoperative morbidity.

This study is designed with the flexibility to open new treatment arms as novel treatment combinations become available and to close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination.

Given the high rate of recurrence and poor prognosis for patients with locally advanced, resectable, HPV-negative SCCHN with current SOC and the safe and tolerable profile of neoadjuvant treatment with CIT monotherapy, combination CIT, or combinations of CITs with chemotherapy, without delaying surgery, in clinical studies that have read out to date, this population and clinical setting are considered appropriate for trials of novel therapeutic candidates.

In addition, based on the data generated to date for CPI monotherapy in SCCHN as well as for the combination of atezolizumab and tiragolumab in SCCHN and other solid tumors, only patients with PD-L1–positive tumors will be enrolled in this study.

The target and proposed mechanism-of-action classification for each investigational medicinal product (IMP) are presented in Table 1. The comparator and experimental treatment regimens are described in Section 3.1 (see also Table 1). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental IMPs, are provided in the respective appendix for each treatment arm, as outlined in Appendix 8 through Appendix 11.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Immune checkpoint inhibitor (PD-L1 antagonist)
Tiragolumab	TIGIT	Immune checkpoint inhibitor (TIGIT antagonist [a])
Carboplatin	DNA	Alkylating antineoplastic agent
Paclitaxel	Tubulin	Anti-mitotic antineoplastic agent

IMP = investigational medicinal product; PD-L1 = programmed death–ligand 1; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

[a] Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

1.3 COVID-19 BENEFIT–RISK ASSESSMENT

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

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess whether outcome from COVID-19 is altered by CIT.

Severe COVID-19 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). Although it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection while receiving immune CPI therapies (e.g., atezolizumab, tiragolumab). At this time, there is insufficient evidence for a causal association between immune-CPI therapies and an increased risk of severe outcomes from COVID-19.

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

A number of COVID-19 vaccines have received approval or emergency use authorization.

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

Per recommendations of the National Cancer Comprehensive Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune-CPIs and chemotherapy), 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 CITs (SITC 2020) and chemotherapy. For patients enrolling in this study and receiving cancer immunotherapy, 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 procedures in clinical practice, factors to consider when making the individualized decision for patients receiving cancer immunotherapy, 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 investigators when deciding on administering COVID-19 vaccines (SITC 2020; NCCN 2021). When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of a COVID-19 vaccine is considered a concomitant medication and should be documented as such. Refer to the respective arm-specific appendix (see A9–6 [Atezo + Tiragolumab (Tira)] and A11–6 [Atezo + Tira + Carboplatin/Paclitaxel (CP)]).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of treatment combinations in treatment-naive patients with locally advanced Stage III–IVA resectable SCCHN.

Specific objectives and corresponding endpoints for the study are outlined below (see Table 2).

Table 2 Objectives and Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• pCR, defined as the absence of any viable primary tumor at time of surgical resection, as determined by local pathologic review
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• pRR as determined by local pathologic review. pRR is defined as the proportion of participants with pCR, mPR (≤10% residual viable tumor at the time of surgical resection in the primary tumor), and pPR (≤50% residual viable tumor at the time of surgical resection in the primary tumor). • EFS, defined as the time from randomization to any of the following events (whichever occurs first): – disease progression that precludes surgery, as determined by the investigator according to RECIST v1.1 – local, regional, or distant disease recurrence – death from any cause • RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause • OS, defined as the time from randomization to death from any cause • ORR, defined as the proportion of patients with a complete response or a partial response, as determined by the investigator according to RECIST v1.1, prior to surgery Responses will be assessed and determined according to RECIST v1.1 but are not required to be confirmed by subsequent imaging studies. • Landmark EFS, defined as the time from randomization to any of the following events (whichever occurs first): – disease progression that precludes surgery, as determined by the investigator according to RECIST v1.1 – local, regional, or distant disease recurrence – death from any cause at specified timepoints (1, 2, 3, and 5 years)

ADA=anti-drug antibody; EFS=event-free survival; ORR=objective response rate; OS=overall survival; pCR=pathologic complete response; PK=pharmacokinetic; mPR=major pathologic response; pPR=pathologic partial response; pRR=pathologic response rate; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS=relapse-free survival.

Table 2 Objectives and Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• *To evaluate the efficacy of treatment (cont.)*	• Landmark RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause at specified timepoints (1, 2, 3, and 5 years) • Landmark OS, defined as the time from randomization to death from any cause at specified timepoints (1, 2, 3, and 5 years)
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of treatment	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 • Incidence and nature of Grade ≥3 immune-related adverse events during the first 12 weeks • Rate and duration of delayed surgery due to treatment-related adverse events • Rate of surgical complications, as assessed according to the Clavien-Dindo surgical classification
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
[redacted]	

[redacted]CR=complete response; EFS=event-free survival; mPR=major pathologic response; ORR=objective response rate; OS=overall survival; pCR=pathologic complete response; [redacted]pPR=pathologic partial response; PR=partial response; pRR=pathologic response rate; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS=relapse-free survival.

Table 2 Objectives and Endpoints (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoints
[redacted]	[redacted]
Exploratory Biomarker Objective	**Corresponding Endpoint**
[redacted]	[redacted]

[redacted] CR=complete response; EFS=event-free survival; mPR=major pathologic response; ORR=objective response rate; OS=overall survival; pCR=pathologic complete response; [redacted]pPR=pathologic partial response; PR=partial response; pRR= pathologic response rate; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS=relapse-free survival.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with locally advanced SCCHN. The study will enroll treatment-naive patients with resectable Stage III–IVA HPV-negative, PD-L1–positive SCCHN with measurable disease, as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) who have not received systemic treatment for their disease (e.g., PD-L1/PD-1– and/or CTLA-4–blocking agents or other agents).

This study is designed to establish proof-of-concept clinical data that neoadjuvant treatment is safe and tolerable and does not have a clinically significant negative effect on surgical outcomes in patients with locally advanced, resectable SCCHN. This study

is also designed to evaluate the anti-tumor effects of neoadjuvant treatment with combination treatments, consisting of Atezo + Tira, and Atezo + Tira + carboplatin/paclitaxel (CP), as measured by pCR.

The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status), or introduce additional cohorts of patients with other types of SCCHN.

Eligible patients will be randomized to one of the treatment arms (see Section 4.2).

3.1.2 Treatment Assignment

Patients will be randomly assigned to a comparator arm (Atezo + Tira) or the experimental arm, consisting of Atezo + Tira in combination with carboplatin and paclitaxel (Atezo + Tira + CP).

Details on the treatment regimens are provided in the respective appendices, Appendix 8 through Appendix 11, and as specified in Table 3 and Figure 1.

Approximately 12–90 patients will be enrolled in the study. Enrollment in the experimental arms will take place in two phases: a preliminary phase, followed by an expansion phase. Approximately up to 20 patients will be enrolled in each treatment arm during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase.

The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with insufficient clinical activity or unacceptable toxicity will not be expanded. Additional patients may be enrolled to ensure balance across treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable additional subgroup analyses. New experimental arms may be added during the study by amending the protocol.

The randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), provided that the likelihood of a patient being allocated to the comparator arm is no more than 50%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for enrollment in a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 3 Treatment Regimens

Study Treatment [a]	Number of Patients (Random Assignment) [b]		Appendix
	Preliminary Phase	Expansion Phase [c]	
Atezo + Tira [d]	Variable [d]		Appendix 9
Atezo + Tira + CP	20 [e]	25	Appendix 11

Atezo = atezolizumab; C = carboplatin; P = paclitaxel; Tira = tiragolumab.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all experimental arms may not be open for enrollment at the same time.

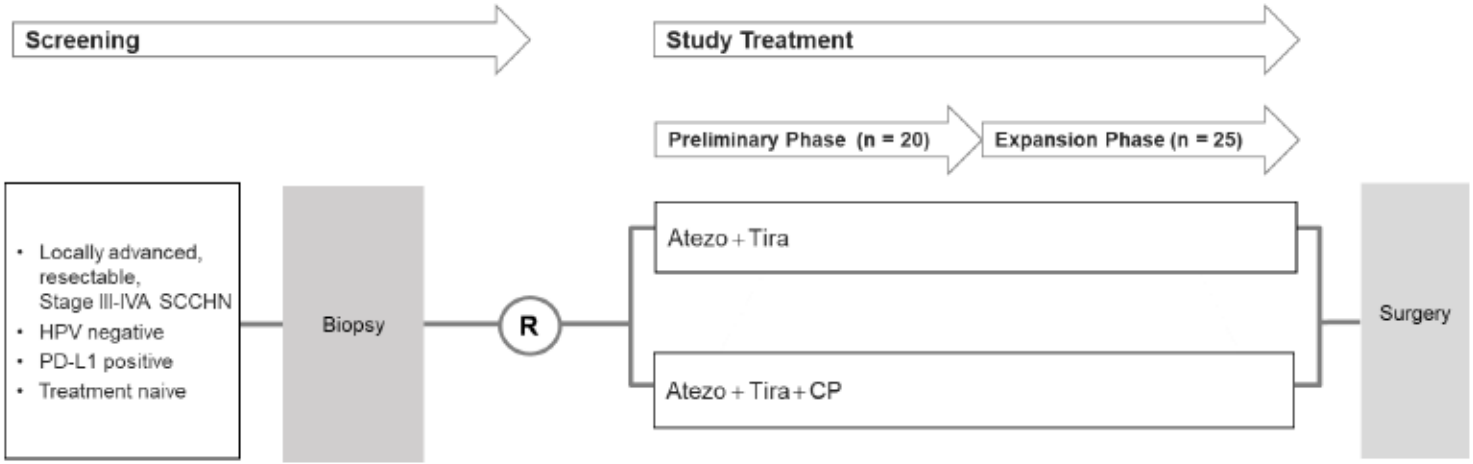
[b] The randomization ratio will depend on the number of experimental arms that are open for randomization (e.g., if an arm is added or randomization into an arm is suspended pending analysis of results from the preliminary phase), provided that the likelihood of a patient being allocated to the comparator arm is no more than 50%. See Section 4.2 for more information.

[c] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

[d] Atezo + Tira is the comparator arm. If no new experimental arms are added in the future, a maximum of 45 patients will be enrolled in Atezo + Tira arm.

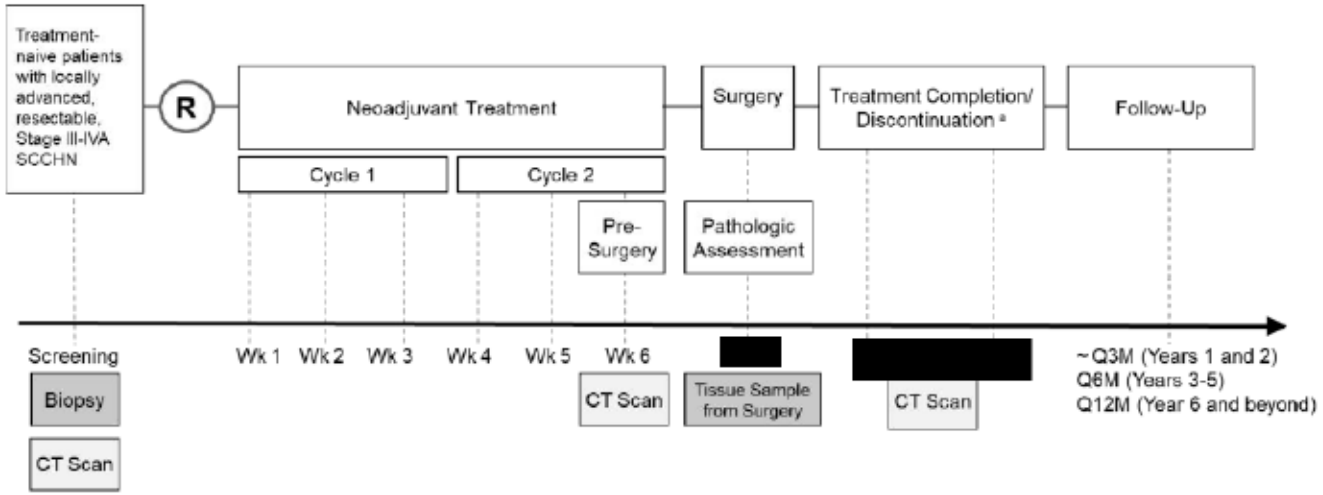
[e] Enrollment will be suspended in the Atezo + Tira and Atezo + Tira + CP arms to allow for a safety evaluation in a minimum of 6 patients (see Section 3.1.3).

Figure 1 Study Schema



Atezo = atezolizumab; CP = carboplatin and paclitaxel; HPV = human papillomavirus; PD-L1 = programmed death–ligand 1; R = randomization; SCCHN = squamous cell carcinoma of the head and neck; Tira = tiragolumab.

Figure 2 Detailed Study Schema



CT=computed tomography; Q3M=every 3 months; Q6M=every 6 months; Q12M=every 12 months; R=randomization; SCCHN=squamous cell carcinoma of the head and neck; *Wk =week*.

[a] At the discretion of the investigator, patients will start adjuvant therapy outside of this study, commencing between [redacted] and after treatment completion/discontinuation visit.

Patients in the comparator arm and the experimental arms will receive neoadjuvant treatment during a 6-week period. After completion of neoadjuvant treatment or in the event of discontinuation because of toxicity and in absence of disease progression, patients will undergo surgery at [redacted] At the discretion of the investigator, patients will subsequently start adjuvant SOC treatment outside of this study between [redacted] and after the treatment completion/discontinuation visit (see Figure 2). For patients who discontinue treatment because of unacceptable toxicity, please refer to Section 3.1.4.

Because of the possibility of an initial increase in the size of metastatic lymph nodes caused by immune-cell infiltration in the context of a T-cell response (termed pseudoprogression) with CITs, suspected clinical or radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment until surgery. Prior to discontinuation of study treatment and/or cancellation of surgery, progression should be confirmed by biopsy or repeated radiographic assessment by an additional expert reviewer. All patients are expected to proceed with surgery, provided that there are no distant metastases and the surgeon considers the disease to be completely resectable.

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 for medical conditions that the investigator or Sponsor determines may jeopardize a patient's safety if he or she continues in the study.

3.1.3 Safety Evaluation Phase

To evaluate the toxicities of the experimental treatments in the neoadjuvant setting, enrollment will be suspended after approximately [redacted] patients have been enrolled in a given arm to allow for a safety evaluation of that arm.

The safety evaluation will be based on safety data from a minimum of [redacted] patients who receive at least one dose of treatment (i.e., one dose of each agent for a given combination) and who have completed the safety follow-up assessments until surgery. Notably, timely conduct of surgery is an indicator of treatment tolerability.

The Sponsor will use an adaptive approach for the continuous safety evaluation during the study (see Section 3.1.3.1 through Section 3.1.3.4).

During the [redacted]-patient safety evaluation phase [redacted] if ≥30% of patients experience one or more of the events listed in Section 3.1.3.4 that are considered by the investigator to be at least possibly related to study treatment, enrollment in that combination arm will be paused while the Sponsor evaluates the benefit–risk profile of treatment. If no new safety signals are detected, enrollment will resume in that arm.

3.1.3.1 Preliminary Phase A

During preliminary Phase A (from n=7 to n=10), if ≥30% of patients experience one or more of the events listed in Section 3.1.3.4 that are considered by the investigator to be at least possibly related to study treatment, enrollment in that combination arm will be paused while the Sponsor evaluates the benefit–risk profile of treatment. If no new safety signals are detected, enrollment will resume in that arm.

3.1.3.2 Preliminary Phase B

During preliminary Phase B (from n=11 to n=20), if ≥25% of patients experience one or more of the events listed in Section 3.1.3.4 that are considered by the investigator to be at least possibly related to study treatment, enrollment in that combination arm will be paused while the Sponsor re-evaluates the benefit–risk profile of treatment. If no new safety signals are detected, enrollment will resume in that arm.

3.1.3.3 Expansion Phase

During the expansion phase, if ≥20% of patients (from n=21 to n=45) experience one or more of the events listed in Section 3.1.3.4 that are considered by the investigator to be at least possibly related to study treatment, enrollment in that combination arm will be paused while the Sponsor evaluates the benefit–risk profile of treatment. If no new safety signals are detected, enrollment will resume in that arm.

3.1.3.4 Events Potentially Triggering a Pause in Enrollment

The following events can potentially trigger a pause in enrollment in a given combination arm if considered by the investigator to be at least possibly related to study treatment:

- A Grade ≥3 treatment-related adverse event that does not improve (with or without treatment) to Grade 2 or better within 2 weeks
- A treatment-related adverse event causing a >2-week delay in surgery (from the planned surgery date)
- A treatment-related serious adverse event
- A treatment-related adverse event that requires permanent discontinuation of study treatment
- Death, except deaths that are incontrovertibly related to disease progression or the result of extraneous causes such as accidents

If no new safety signals are detected, enrollment will resume in that arm.

3.1.4 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). [redacted]

Patients will receive neoadjuvant treatment for two cycles (6 weeks) and will undergo surgery at [redacted]

All patients are expected to proceed with surgery, provided that there are no distant metastases and the surgeon considers the disease to be completely resectable. Pathological response will be assessed by local pathologic review.

Patients who discontinue treatment because of unacceptable toxicity and who continue to be candidates for curative surgery will be eligible for surgery after the adverse event has resolved and re-staging confirms Stage III–IVA disease. If patients have confirmed disease progression, patient management and treatment selection will be at the discretion of the treating physician. Such patients will remain in the study for follow-up.

Patients will undergo radiological tumor assessments (with or without endoscopy at the investigator's discretion) at Week 6 [redacted] prior to surgery (see Section 3.1.4 for details). Response will be assessed and determined by the investigator in accordance with RECIST v1.1, but confirmation by subsequent imaging studies is not required (see Appendix 1).

For all patients, blood samples will be collected at baseline and during the study for biomarker research, including [redacted]

Tumor samples will be collected at baseline and during the study for biomarker assessments. Baseline tumor tissue samples will be collected from all patients by biopsy of the primary tumor or a metastatic lymph node at screening. If a biopsy has been performed for the initial diagnosis of SCCHN prior to the patient entering screening, this tissue sample can be used as a baseline biopsy as long as it meets the quality criteria in this protocol (see Section 4.5.11). These samples will be utilized for biomarker research (see the [redacted] and details on tissue sample collection in Section 4.5.11). If possible, baseline screening samples should be obtained after all other screening assessments have been evaluated for eligibility.

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and the other therapeutic agents, blood samples will be obtained at specified timepoints prior to and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in Sections A9–6 (Atezo+Tira) and A11–6 (Atezo+Tira+CP).

3.1.5 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from clinical science, safety science, and biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, or enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of available data. Ad-hoc meetings may be called in addition to scheduled meetings to provide recommendations on management of any new safety issues. Specific operational details such as the Committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in the IMC Charter.

3.1.6 Scientific Oversight Committee

A Scientific Oversight Committee will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the Scientific Oversight Committee will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data to be evaluated by the Scientific Oversight Committee will include demographic, adverse event, serious adverse event, and relevant laboratory data. The Committee may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.1.7 Local Pathology Review

Resection tissue and other clinical data as needed for the primary and secondary efficacy analyses will be reviewed by the local pathology lab. Patients will be categorized as achieving a pCR (no *residual viable tumor* on hematoxylin and eosin evaluation of completely resected tumor specimens, including all sampled lymph nodes) (mPR, ≤10% *residual viable tumor*), or pPR (>10% to 50% *residual viable tumor*) (Weissferdt et al. 2018) based on immune-related *pathological response* criteria (Cottrell et al. 2018; Stein et al. 2020).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit, including survival follow-up visits conducted by telephone or in the clinic.

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

3.3 DURATION OF PARTICIPATION

The total duration of study participation for each individual from screening until treatment completion visit and start of adjuvant treatment is expected to be approximately 17 weeks (not including follow up) and includes:

- Screening: Days –28 to –1
- Treatment period: 13 weeks; patients will receive neoadjuvant treatment during a 6-week period and will undergo surgery at [redacted] After surgery and prior to commencing adjuvant treatment, treatment completion will be performed between [redacted]

Participants may continue on the study, including the following visits:

- During the follow-up period, disease status should be clinically evaluated and documented approximately every 3 months (according to local or institutional guidelines and standards) for the first 2 years; every 6 months during Years 3, 4, and 5; and once a year during Year 6 and subsequent years
- Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

This study will enroll treatment-naive patients with resectable Stage III–IVA SCCHN with measurable disease (according to RECIST, v1.1). Enrolled patients must not have received prior immunotherapy for their disease.

Similar patient populations were enrolled in the perioperative studies discussed in Section 1.1.2.1 of this protocol. Neoadjuvant therapy was found to have a clinically meaningful benefit (Leidner et al. 2021; Schoenfeld et al. 2020; Uppaluri et al. 2020; Wise-Draper et al. 2021). In addition, the safety profile of treatment was found to be tolerable using an optimized treatment schedule.

Despite the recently demonstrated benefit of checkpoint inhibition therapy, there is a continuing need for treatment regimens that are more efficacious (i.e., broader and deeper pathologic response in the surgical specimen) and improved tolerability for patients with resectable SCCHN. The treatment options in this study are expected to stimulate the immune system by different mechanisms (Appendix 9 [Atezo + Tira] and A11–1 [Atezo + Tira + CP] for more details). The aim is to extend the benefit of CIT in the perioperative setting beyond that of current checkpoint inhibition in patients with locally advanced SCCHN.

3.4.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hale and Fink 2010). In Study PCD4989g (atezolizumab monotherapy), evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells.

Because of the possibility of an initial increase in the size of metastatic lymph nodes caused by immune-cell infiltration in the context of a treatment-elicited T-cell response in the absence of unacceptable toxicity, patients who meet the criteria for disease progression in the target lymph node metastases according to RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment until surgery. However, the appearance of novel, previously undetected non–lymph node lesions may indicate that a patient has in fact been understaged and instead presents with more advanced or Stage IV disease. Because of the potential for a response after pseudoprogression, this study will allow patients randomly allocated to the immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged by the investigator to be favorable (for the criteria, see Section 3.1.2). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.2 for details).

3.4.3 Rationale for Neoadjuvant Treatment of SCCHN

Neoadjuvant therapy has several potential advantages in this patient population. Neoadjuvant immunotherapies will enhance systemic T-cell responses for tumor-specific antigens prior to surgery (Topalian et al. 2020). The premise of neoadjuvant immunotherapy is to use the existing tumor mass as an in-situ source of tumor-specific antigens to enhance systemic immunity by means of dendritic cell antigen presentation to rejuvenate T cells and priming, especially for cytotoxic T cells (Topalian et al. 2020). This enhanced function acts to destroy micrometastasis in clinically advanced tumors, decreasing locoregional or distant metastasis after primary therapies. Drug exposure during the time the majority of the tumor mass is still present and may therefore potentially induce a stronger and broader tumor-specific T-cell response (Blank et al. 2018). In addition, neoadjuvant therapy may allow investigators to determine therapy efficacy in individual patients, which could guide the use of additional adjuvant therapy, if needed. Thus, studies of previously untreated tumors may enable establishment of predictive biomarkers used to select appropriate patients and to define mechanistic pathways.

Neoadjuvant therapy is also expected to reduce tumor burden before surgery, and pathologic response data could be used as surrogate outcome markers for relapse-free survival (RFS) and OS. Preclinical data provided support for the superior activity of T cell–checkpoint blockade when given before surgery (Liu et al. 2016).

Moreover, clinical data generated with neoadjuvant therapy (described in Section 1.1.2.1) indicate that neoadjuvant therapy with a CIT combination as well as CIT in combination with chemotherapy are safe and promising approaches that could potentially change the current SOC in this population with high medical need.

3.4.4 Rationale for Pathologic Response Rate as the Primary Endpoint

pCR and mPR are widely used as surrogate clinical endpoints for long-term survival (Junker et al. 1997; Weissferdt et al. 2010; von Minckwitz et al. 2012; Cortazar et al. 2014). pCR means the ablation of all cancer cells in resected tumor after the treatment. In contrast, mPR represents ≤10% of *residual viable tumor* (Hellman et al. 2014).

Previously reported data from neoadjuvant studies in SCCHN show that single-agent treatments as well as combined CPI treatment can induce pCRs and do not delay surgery; furthermore, perioperative studies endorse *pathological response* as a potential surrogate outcome marker for DFS in patients with intermediate- and high-risk SCCHN (Wise-Draper et al. 2020, 2021).

However, the establishment of the best pathological method to evaluate the response of neoadjuvant immunotherapy is still evolving given that the ultimate clinical effect of histologic changes is not understood.

[redacted]

[redacted]

[redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to qualify for the study:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Ability to comply with the protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 3)

- Histologically confirmed, resectable Stage III–IVA SCCHN

  Staging should be based on the AJCC, 8th edition (Amin et al. 2017)/Union Internationale Contre le Cancer staging system.

  Patients with a primary site of tumor in the nasopharynx or salivary glands of any histology are not eligible.

  [redacted]
- Eligible candidate for R0 resection with curative intent at the time of screening
- HPV-negative test for oropharyngeal carcinoma, [redacted]
- Measurable disease (at least one target lesion), as assessed according to RECIST v1.1 (see Appendix 1)
- PD-L1 expression, defined as a CPS ≥ 1 result [redacted]
- Availability of a representative tumor specimen that is suitable for [redacted]
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

  - Creatinine ≤1.5× ULN or creatinine clearance ≥30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin ≥25 g/L (≥2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR and aPTT ≤1.5× ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen (i.e., no new thrombosis, thromboembolic event, or bleeding episode within 3 months prior to study treatment start)
- Negative HIV test at screening with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count≥200/μL, and have an undetectable viral load.

[redacted]

- *Negative hepatitis B surface antigen (HBsAg) test at screening*
- *Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:*
  - *Negative total hepatitis B core antibody (HBcAb)*
  - *Positive total hepatitis B core antibody (HBcAb) followed by a negative quantitative hepatitis B virus (HBV) DNA*
  - [redacted]
- [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse and donating eggs) or use contraceptive measures, as outlined for each specific treatment arm in Appendix 8 through Appendix 11
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 8 through Appendix 11

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- HPV-positive oropharyngeal cancer, as determined locally by p16 IHC, in situ hybridization, or by polymerase chain reaction–based assay
- Distantly metastasized SCCHN
- Any prior therapy for SCCHN, including immunotherapy, chemotherapy, or RT
- Prior treatment with any of the protocol-specified study treatments
- Treatment with investigational therapy within 42 days prior to initiation of study treatment
- Treatment with systemic immunostimulatory agents (including, but not limited to, within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunosuppressive medication (including, but not limited to, , and within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  -
  -
  -
- 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 or within 5 months after the final dose of study treatment

- Active or history of autoimmune disease or immune deficiency, [redacted] with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  - Rash must cover < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- 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 computed tomography (CT) scan
- History of malignancy other than SCCHN 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.
- Active tuberculosis
- 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, may impact patient safety
- Treatment with therapeutic or prophylactic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  [redacted]

- Significant cardiovascular disease such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure other than tumor resection, during the study

[redacted]

- 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, impair the ability of the patient to participate in the study, or renders the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Known intolerance to any of the drugs required for premedication (acetaminophen, ranitidine, diphenhydramine, and methylprednisolone)
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

[redacted]

- Eligible only for the comparator arm
- Active Epstein-Barr virus (EBV) infection or known or suspected chronic active EBV infection at screening

[redacted]

4.1.2.1 Specific Exclusion Criteria for Atezo+Tira+CP Arm

Patients who meet any of the following criteria will be excluded from the Atezo+Tira+CP arm:

- Known severe allergy or hypersensitivity to paclitaxel
- Known severe allergy or hypersensitivity to platinum or platinum-containing compounds
- Known history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate)
- Creatinine clearance <45 mL/min (calculated using the Cockcroft-Gault formula)

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment through an interactive web-based response system (IxRS).

This study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment during the study. The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), provided that the likelihood of a patient being allocated to the comparator arm will be no more than 50%. The randomization ratios may be altered to increase enrollment in a particular arm.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Section 4.1.2.

Patients who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses.

Additional patients may be enrolled to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 3.

4.3.1 Investigational Medicinal Product Handling and Accountability

The IMPs for this study are atezolizumab, tiragolumab, carboplatin, and paclitaxel. Appendix 12 identifies all investigational medicinal products, non-investigational medicinal products (NIMPs), and auxiliary medicinal products (AxMPs) for this study. All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. 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 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 will be returned to the Sponsor (if supplied by 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 a drug accountability log.

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

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments 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, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Details on concomitant therapy, prohibited food, and additional restrictions are provided in the respective appendix for each treatment arm (see Sections A9–4.2 [Atezo + Tira] and A11–4.2 [Atezo + Tira + CP]).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for screening in Appendix 6 and for each treatment arm (see Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]). All activities must 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 infusion; dosing will occur only if clinical assessment and local laboratory test values are acceptable.

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) and may be obtained more than 28 days before initiation of study treatment. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

Patients who do not meet the criteria for participation in this study may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening.

Results of SOC tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1 may be used as outlined in the schedule of activities (see Appendix 6 [screening]). Such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. The patient's molecular profile for SCCHN, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time 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.

Refer to the schedule of activities for information about the timing of medical history, molecular profile, concomitant medication, and demographic data collection (see Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include evaluations as per clinical standard (e.g., 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 electronic Case Report Form (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.

Height will be recorded at screening. Weight will be recorded at *screening and* specified timepoints during the study.

Refer to the schedule of activities for information about the timing of physical examinations (see Appendix 6 [screening], Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured within 60 minutes prior to administration of each study treatment and, if clinically indicated, during or after treatment administration *(see Table A9-3 [Atezo + Tira], Table A11-2 and Table A11-3 [Atezo + Tira + CP])*. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 6 [screening], and Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Electrocardiograms

A 12-lead ECG will be performed at screening, as outlined in the schedules of activities (see Appendix 6 [screening], and Sections A9–6 [Atezo+Tira] and A11–6 [Atezo+Tira+CP]) *and as clinically indicated*. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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.

4.5.6 Tumor and Response Evaluations

4.5.6.1 Radiographic Procedures at Screening

All measurable and evaluable lesions should be assessed and documented at screening as outlined in the schedule of activities (see Appendix 6 [screening]).

Screening assessments must include CT scans (with oral and/or IV contrast) or magnetic resonance imaging (MRI) scans of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck (from the base of the skull to clavicle). If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest and abdomen may be performed, and MRI scans with contrast of the head and neck, abdomen, and pelvis (as applicable *and/or per clinical standard*) must be performed.

A CT scan with contrast or MRI scan of the head must be performed at screening to evaluate the presence of central nervous system (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. Patients with CNS metastases are not eligible for the study

Bone scans should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease may be used according to RECIST v1.1 (see Appendix 1).

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Tumor assessments performed as SOC prior to obtaining informed consent and within 28 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/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations as outlined in Section 4.5.6.2. 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).

4.5.6.2 Tumor and Response Evaluations

Patients will be assessed for pathologic and radiologic response to treatment. Patients will undergo pathological tumor assessments at surgery. Surgery should be performed as planned if a patient is receiving corticosteroids or other anti-inflammatory drugs for the management of immune-mediated adverse events, provided these are being given at a stable or tapering dose and the severity of adverse events is Grade 2 or better. Surgery may be delayed for up to 2 weeks if study treatment–related adverse events have not improved sufficiently at the time of planned surgery (see Section 3.1.3). PR will be determined by local pathologic review.

Patients will undergo radiographic tumor assessments, as assessed by the investigator according to RECIST v1.1, at baseline and after neoadjuvant treatment ≤7 days before surgery, as outlined for each arm in the schedules of activities (see Sections A9–6 [Atezo+Tira] and A11–6 [Atezo+Tira+CP]). At the treatment completion or discontinuation visit between [redacted] disease status will be assessed by radiographic tumor assessments for the absence of recurrent disease *and should include a CT scan or MRI*.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to study treatment administration.

Disease Follow-Up and Confirmation of Disease Progression or Recurrence

During the neoadjuvant treatment, diagnosis of disease progression should be confirmed by clinical, laboratory, radiological, and/or histological findings. After surgery, prior to commencing adjuvant treatment, *the first* tumor assessment will be performed between [redacted] to conclude the neoadjuvant therapy or surgical intervention window *and should include a CT scan or MRI*. Thereafter, during the *follow-up phase*, all patients must be followed outside the study for assessment of disease recurrence and survival, as outlined for each arm in the schedules of activities (see Sections A9–6 [Atezo+Tira] and A11–6 [Atezo+Tira+CP]).

During the follow-up period, disease status should be clinically evaluated and documented approximately every 3 months (according to local or institutional guidelines and standards) for the first 2 years; every 6 months during Years 3, 4, and 5; and once a year during Year 6 and subsequent years. In addition, liver function tests, bone scans, chest X-ray and diagnostic CT scan, liver imaging, endoscopy, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

The diagnosis of a progression or recurrence should made based on the investigator's discretion and/or the procedures listed below. It should be confirmed histologically whenever clinically possible. The earliest date of diagnosis of disease progression or recurrent disease should be used and recorded. The date should be based on objective clinical, radiologic, histologic, or cytologic evidence. Recurrent disease includes local, regional, or distant recurrence.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events at follow-up are provided below. Documentation of recurrence will require specification of all sites involved to establish the pattern of recurrence.
In addition to investigator's judgment, the following criteria for treatment failure constitute acceptable evidence of disease recurrence:

- Lung: positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- Liver: positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- CNS: positive brain CT or MRI scan or cerebrospinal cytology
- Lymph node recurrence: positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- Bone and other organs: positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease identified on two different radiologic studies (i.e., positive nuclear bone scan or positron emission tomography scan and contrast gastrointestinal series or ultrasound, X-ray, or CT scan of abdomen for abdominal disease)

4.5.7 Classification of Surgical Complications

Surgical complications will be scored according to Clavien-Dindo classification (see Appendix 2). Complication rates for every grade will be reported and scored for patients who undergo surgery, as outlined for each arm in the schedule of activities (see Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

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

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to develop adverse events,

can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood 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 WGS or WES is contingent upon the review and approval of the exploratory research by each site's *Institutional Review Board* (IRB)/*Ethics Committee* (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.8) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or that are predictive of 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 WGS or WES will 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 4.5.11 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.9 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. Patients who consent to optional biopsies may undergo additional biopsies during treatment biopsies at any other time at the investigator's discretion and if deemed clinically feasible. Please refer to Section 4.5.11.2 for more details.

Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.
For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

An Informed Consent Form with 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.

Samples may be used for exploratory biomarker research as described in Section 4.5.11.2. Refer to Section 4.5.11.2 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 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 biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, and peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of biomarkers assays, 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 used to achieve 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 assays and establish the performance characteristics of these assays

4.5.10.2 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 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 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

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

- [redacted]

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

4.5.10.4 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 exploratory 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.

4.5.10.5 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 specimens 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 specimens. 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 specimens and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent from the RBR 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 samples, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, 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 from the RBR does not constitute withdrawal from this study.

4.5.10.7 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.

4.5.11 Laboratory, Biomarker, and Other Biological Samples

4.5.11.1 Local Laboratory Assessments

For information about the timing of local laboratory assessments, please refer to the schedule of activities for screening (see Appendix 6 [screening] or the appropriate treatment arm (Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered SOC in the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, amylase and lipase (on Day 1 of each treatment cycle), and lactate dehydrogenase
- Lipid panel: triglycerides, high-density lipoprotein, and low-density lipoprotein
- Coagulation: INR and aPTT
- Thyroid-function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- C-reactive protein
- [redacted] serology, unless not permitted per local regulations

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Newly collected tumor tissue sample obtained at baseline or archival [redacted] or for determination of PD-L1 expression, defined as a [redacted]
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During follow-up, pregnancy tests will be performed at 6 months.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.
- Urinalysis: pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted

4.5.11.2 Central Laboratory Assessments

For information about the timing of central laboratory assessments, please refer to the schedule of activities for screening (Appendix 6) or the appropriate treatment arm (see Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- [redacted]
- [redacted]
- [redacted]
- [redacted] for exploratory research on biomarkers, including [redacted]
- Archival [redacted] or newly collected [redacted] tumor tissue sample obtained at baseline for determination of PD-L1 expression. PD-L1 expression, defined as a CPS ≥ 1 result [redacted] Tissue may also be used for exploratory research on biomarkers.

  [redacted]

  [redacted]

  Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.
- For exploratory biomarker research: [redacted]

  [redacted]

[redacted]

- Optional biopsies during treatment may be performed at the investigator's discretion and if deemed clinically feasible for exploratory research on biomarkers at the following timepoints:
  - Between Cycle 1 and Cycle 2 (≥ 10 days after Day 1, Cycle 1)
  - At the time of disease recurrence
  - At any other time at the investigator's discretion
- Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy preferred

Table 4 Overview of Tissue Samples

Timepoint	Sample Type	Requirement
Screening	Archival tissue or fresh biopsy	Mandatory
Surgery [a]	Fresh tissue from surgery	Mandatory
Between Cycle 1 and Cycle 2 (≥ 10 days after Day 1, Cycle 1)	Fresh biopsy	Optional
At the time of disease recurrence	Fresh biopsy	Optional
At any other time at the investigator's discretion	Fresh biopsy	Optional

[a] Refer to Sections 3.1.2 and 3.1.4 window.

Exploratory biomarker research may include, but will not be limited to, [redacted]

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 4.5.10), biologic samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- [redacted] therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- [redacted] will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks or remaining freshly collected tissue submitted to the central lab for determining PD-L1 status will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

Given the complexity and exploratory nature of biomarker analyses, 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.

4.6 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 study treatment, 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
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Confirmed disease progression or dissemination prior to surgery

  Patients who discontinue study treatment early because of an unacceptable toxicity should continue to be followed for both resolution of toxicity and disease recurrence as outlined in the schedule of activities (Sections A9–6 [Atezo + Tira] and A11–6 [Atezo + Tira + CP]).

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

Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for an end of treatment visit 3–6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion or treatment discontinuation visit ≤ 30 days after the final dose of study treatment. For patients who progress or have loss of clinical benefit, the visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit.

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 3 months 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 study, the study staff may use a public information source (e.g., country records) to obtain information about survival status only. For an experimental arm in which all patients discontinue treatment and pass the safety follow-up window, as well as approximately 80% of patients discontinue from the study *or all patients have been followed up for at least 2 years, whichever occurs first,* the Sponsor may conclude the arm *(all remaining patients in that arm will be discontinued from the study).*

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
- Loss to follow-up
- 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. Patients who withdraw from 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

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm in Appendix 9 (Atezo+Tira) and Appendix 11 (Atezo+Tira+CP).

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 COVID-19 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per the investigator's judgment. If a diagnosis of COVID-19 is confirmed, disease should be managed as per local or institutional guidelines.

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 5.3.6.

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 Section 5.3.5.9 and Section 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 drug
- 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 drug
- 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 each treatment arm are listed in the respective appendix for that treatment arm (see in Appendix 8 through Appendix 11).

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 5.3.6–5.6.

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 drug, 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 or until initiation of new systemic anti-cancer therapy, whichever occurs first, 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 or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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 non-directive 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 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 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 (v5.0)=National Cancer Institute Common Terminology Criteria for Adverse Events (Version 5.0).

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]

[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 the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug 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 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug 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 the study drug, 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 the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
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 the study drug (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 the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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, the time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis (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 a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 7.

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., ALP 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 (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 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× baseline value) in combination with either an elevated total bilirubin (>2× 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× baseline value in combination with total bilirubin >2×ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST >3× baseline value 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) 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 5.3.6).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. 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 disease 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).

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 Squamous Cell Carcinoma of the Head and Neck

Events that are clearly consistent with the expected pattern of progression 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 RECIST v1.1. 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., 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

5.3.6 Special Situations: Accidental Overdose And/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 (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of study drug, special situations associated with atezolizumab and tiragolumab and any associated adverse events will be reported until [redacted] days; after the final dose of study drug.

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

Special situations and any associated adverse events should be reported within [redacted] days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section 5.4.2.

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 drug:

- 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, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting 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 Drug Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report by means of 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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

The reporting requirements for pregnancies are presented in the arm-specific appendices (see in Appendix 8 through Appendix 11).

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 adverse event reporting period (defined in Section 5.3.1), 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, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

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 (defined as [redacted] days after the final dose of study treatment or until initiation of new, systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. *After the end of the reporting period for non-serious adverse events (defined as [redacted] days after the final dose of study treatment), all treatment-related non-serious adverse events that lead to surgery delay will continue to be reported until [redacted] days after the final dose of study treatment.*

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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

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:

- Atezolizumab Investigator's Brochure
- Tiragolumab Investigator's Brochure
- Carboplatin Ireland Summary of Product Characteristics
- Paclitaxel Ireland Summary of Product Characteristics

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen and safety analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually receive. Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on treatments or treatment combinations when administered to patients with SCCHN. Approximately 12–90 patients will be randomly allocated to the comparator and experimental arms during the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm. Patient disposition will be summarized by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, duration of malignancy, metastatic disease site [if applicable], and baseline ECOG Performance Status) will be summarized overall and by treatment arm.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is pCR (complete absence of viable tumor in the treated tumor bed, as determined by local pathologic review) at time of surgery (see Sections 3.1.2 and 3.1.4). pCR will be assessed after completion of neoadjuvant treatment at the time of surgery. The pCR rate is defined as the proportion of patients who achieve a pCR. The pCR rate will be calculated for each arm along with 95% CIs. The difference in the pCR rates between the experimental arms and the comparator arm will also be calculated along with 95% CIs. The 95% CI for rates will be estimated using Clopper-Pearson method, and the 95% CI for difference in rates will be estimated using Wald method with continuity correction. *Patients with missing or no pathologic response assessment will be classified as non-responders.*

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are pRR at time of surgery, as determined by local review, EFS, RFS, OS, ORR prior to surgery, landmark EFS, landmark RFS, and landmark OS at specific timepoints (1, 2, 3, and 5 years).

The pRR is defined as the proportion of patients who achieve a pCR (complete absence of viable tumor in the treated tumor bed), mPR (≤10% of viable tumor in the treated tumor bed), and pPR (≤50% of the treated tumor bed occupied by viable tumor cells), as determined by local pathologic review. The pRR will be calculated for each arm along with 95% CIs. The difference in pRR between the experimental arms, and the comparator arm will also be calculated along with 95% CIs. The 95% CI for rates will be estimated using Clopper-Pearson method, and the 95% CI for difference in rates will be estimated using Wald method with continuity correction.

EFS is defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1 (see Section 4.5.6) and local, regional, or distant disease recurrence, or death from any cause. Data from patients who have not experienced such events will be censored at the time of the last tumor assessment.

RFS is defined as the time from surgery to the first documented recurrence of disease or death from any cause. For patients who do not have documented recurrence of disease or have died, RFS will be censored at the day of the last tumor assessment.

OS is defined as the time from randomization to death from any cause. Data from patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for EFS, RFS, and OS, 95% CIs will be constructed using the Brookmeyer and Crowley method. The rate of EFS, RFS, and OS at specified timepoints will also be estimated using the Kaplan-Meier method, with 95% CIs calculated on the basis of Greenwood's estimate for variance.

The ORR according to RECIST v1.1 will be assessed after completion of neoadjuvant treatment and is defined as the proportion of patients with a complete response or partial response, as determined by the investigator according to RECIST v1.1. Patients with missing or no response assessments will be classified as non-responders. Note that ORR will be determined using unconfirmed preoperative radiologic responses. Although RECIST v1.1 require confirmatory imaging assessments to be completed at least 4 weeks after the initial response, owing to the timing of surgery, such responses cannot be confirmed with subsequent imaging.

The ORR will be calculated for each arm, along with 95% CIs, using the Clopper-Pearson method. The difference in ORR between the experimental arms and the comparator arm will also be calculated, along with 95% CIs. The 95% CI for rates will be estimated using Clopper-Pearson method, and the 95% CI for difference in rates will be estimated using Wald method with continuity correction.

Landmark EFS rates, landmark RFS rates, and landmark OS rates will be estimated for each study arm using the Kaplan-Meier method, with 95% CIs calculated through use of Greenwood's formula.

6.5 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms. Adverse event severity will be graded according to NCI CTCAE v5.0, [redacted] All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.

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

Additionally, the incidence, nature of immune-related adverse events Grade ≥ 3 during the first 12 weeks, and the rate and duration of delayed surgery due to treatment-related adverse events will be summarized by treatment arm. Surgery may be delayed for up to 2 weeks if study treatment–related adverse events have not improved sufficiently at the time of planned surgery (see Section 3.1.3).

Additionally, surgical complications will be scored according to Clavien-Dindo classification (Dindo et al. 2004) (see Appendix 2). Complication rates for every grade will be reported and scored for patients who underwent surgery.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified drugs given either alone or in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm

and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab or other study drug concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters, such as clearance, volume of distribution, and area under the curve–concentration time curve.

The relationship between PK parameters and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity may be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

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

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [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 by means of an 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.

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 on 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, 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 on 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 on 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, Informed Consent Forms, laboratory test results, and medication inventory records, and images, 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.

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.

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 Trial 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) to communicate information that might affect a patient's willingness to continue 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.

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 9.5).

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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 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 9.5).

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.

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.

9.3 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. 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 4.5.11. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. A Scientific Oversight Committee will provide external expert opinions on the safety data collected during the study.

9.4 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). In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be 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.

9.5 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
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; Schwartz et al. 2016) are presented below, with the addition of explanatory text as needed for clarity.

TUMOR MEASURABILITY

At baseline, tumor lesions and lymph nodes will be categorized as measurable or non-measurable 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 ≤ 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 ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 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").

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 non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lungs, 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, positron emission tomography (PET) 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 not usually more than 4 weeks prior to the beginning of 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 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 because 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 (with or without MRI 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 (with or without MRI IV contrast) 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 if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, AND 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 20×30 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 non-measurable), 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 non-target 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, given that 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 is 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 is 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 during 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 the 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 the 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 "unequivocal 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 following criteria used to determine objective tumor response for target lesions are provided:

- 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 a CR or a 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

  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
- 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.

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 a PR or a 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 truly represents new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared as of the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients.

Table A1-1 Criteria for Overall Response at a Single Timepoint

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, non-CR/non-PD, or NE	No	PR
SD	CR, non-CR/non-PD, or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR	NED [b]	No	CR
PR	NED [b]	No	PR
SD	NED [b]	No	SD
NED [a]	Non-CR/non-PD	No	Non-CR/non-PD
NED [a]	CR	No	CR
NED [a]	NE	No	NE
NED [a]	NED [b]	No	NED

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

[a] No target lesions identified at baseline

[b] No non-target lesions identified at baseline.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging or measurement is performed 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 treatment. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A1-1.

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.

Fluorodeoxyglucose (FDG)-PET is **not yet validated** for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.

FDG-PET imaging to identify new lesions is described in the following table.

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT/MRI	Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site. If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date If not, it is not a new lesion.
None	Positive FDG-PET that corresponds to a preexisting site of disease on CT/MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography.

Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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.

Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016; 62:132–7.

Appendix 2
Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are drugs as antiemetic medications, antipyretic medications, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for Grade I complications Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) [a] requiring IC or ICU management
Grade IVa	Single-organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge [b], the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

CNS = central nervous system; IC = intermediate care; ICU = intensive care unit.

[a] Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attack.

[b] For examples of complication grades, see Table 2 in Dindo et al. (2004).

REFERENCE

Dindo D, Demartines N, Clavien PA. Classificiation of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

Appendix 3
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active; able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about 50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair>50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG=Eastern Cooperative Oncology Group.

Appendix 4
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 following table 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 for which the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab and tiragolumab 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 regarding any uncertainty about autoimmune exclusions.

Appendix 5
Anaphylaxis Precaution

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 medications are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

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

PROCEDURES

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

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

Appendix 6
Study Details Specific to Screening

Assessment or Procedure	Protocol Section	Screening Day –28 to Day –1 (unless specified otherwise)
Informed consent	Section 4.5.1	x
Demographics	Section 4.5.2	x
Medical history and baseline conditions		x
Molecular profile of SCCHN (if available)	Section 4.5.2	x
Weight	Section 4.5.3	x
Height		x
Complete physical examination		x
Vital signs	Section 4.5.4	x
12-Lead ECG	Section 4.5.5	x
ECOG Performance Status	Appendix 3	x
PD-L1 testing	Section 4.5.11.1	x
HPV status		x
Baseline tumor assessments	Section 4.5.6	x
Pregnancy test	Section 4.5.11.1	x (blood test) (Day –14 to Day –1)
Urinalysis	Section 4.5.11.1	x (Day –14 to Day –1)
Concomitant medications	Section 4.5.2	x (Day –7 to Day –1)
Adverse events [a]	Section 5	x
Hematology	Section 4.5.11.1	x (Day –14 to Day –1)
Chemistry		x (Day –14 to Day –1)
Lipid panel		x (Day –14 to Day –1)
Coagulation: INR and aPTT		x (Day –14 to Day –1)
TSH, free T3 (or total T3), and free T4		x (Day –14 to Day –1)

Assessment or Procedure	Protocol Section	Screening Day –28 to Day –1 (unless specified otherwise)
C-reactive protein	Section 4.5.11.1	x
Viral serology		x
Lactate dehydrogenase		x
Blood and plasma samples for biomarkers [b]	Section 4.5.11.2	x
Tumor biopsy [b]	Section 4.5.11.2	x

CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; HPV=human papilloma virus; IHC=immunohistochemistry; PD-L1=programmed death–ligand 1; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine.

[a] 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 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.

[b] Screening samples should be obtained, if possible, after all other screening assessments have been evaluated for eligibility.

Appendix 7
Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Toxicities associated or possibly associated with atezolizumab 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.

[redacted]

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

- [redacted]

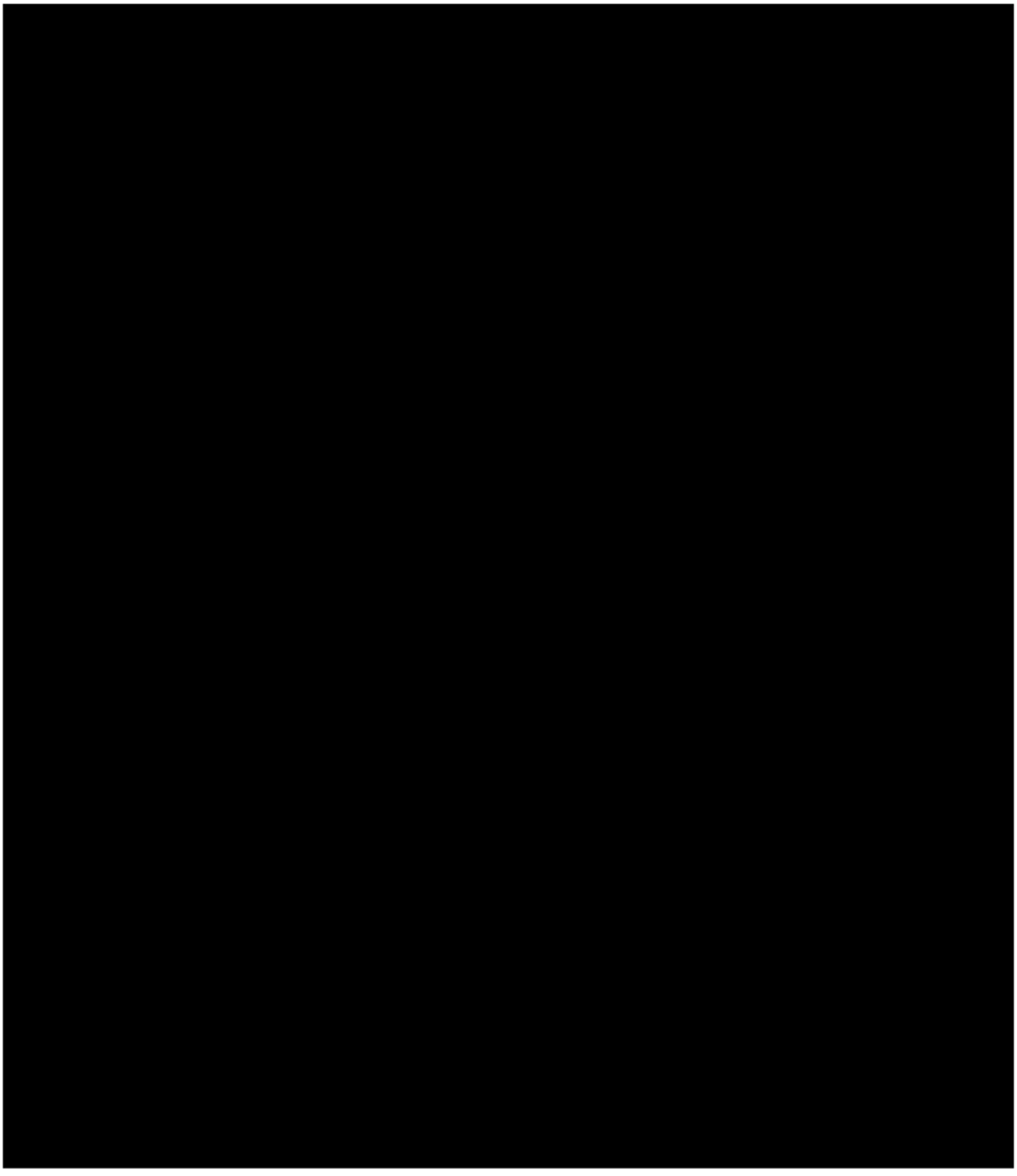
MANAGEMENT GUIDELINES

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 and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

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 A7-1.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A7-2.

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.

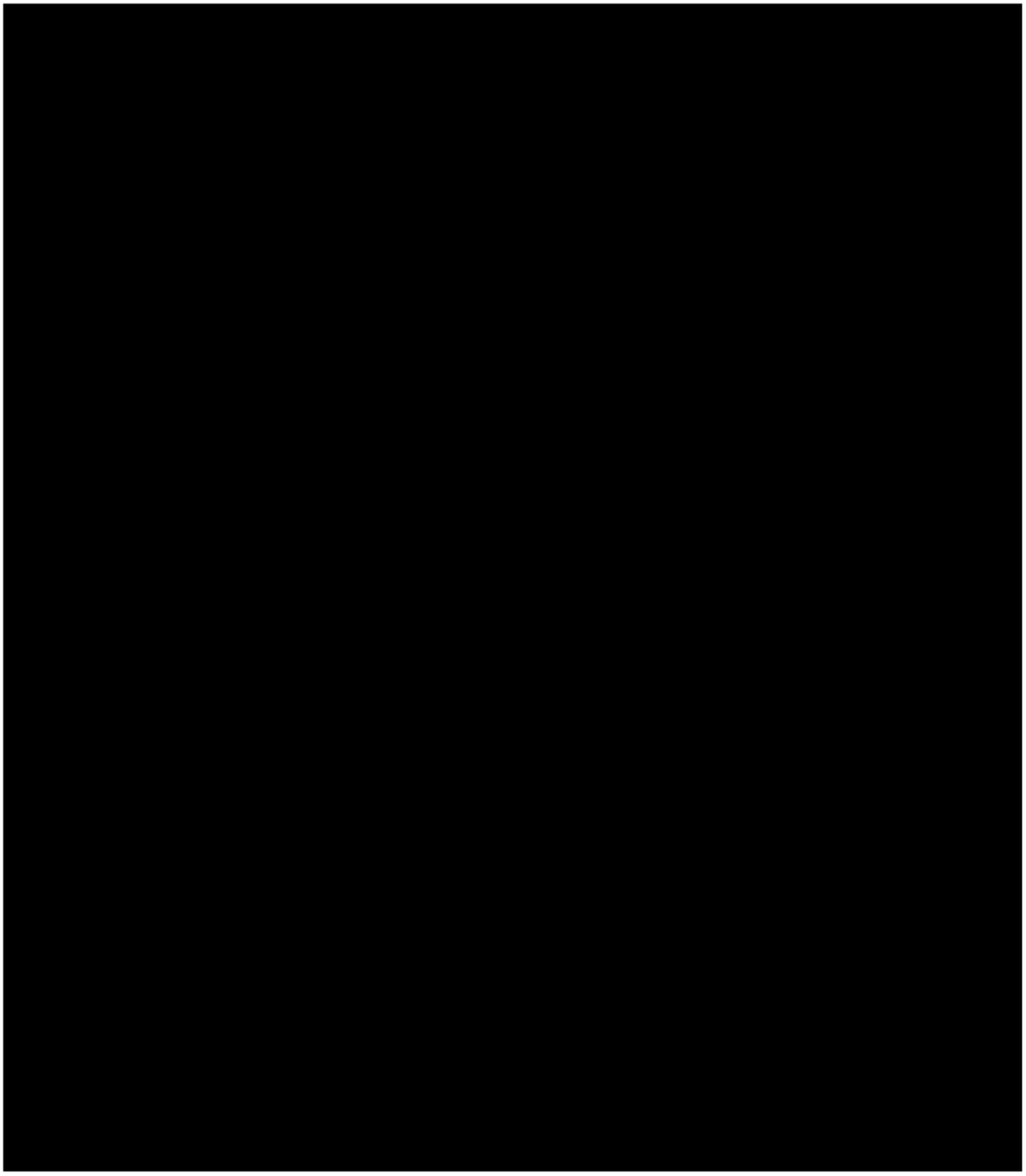
For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

GASTROINTESTINAL EVENTS

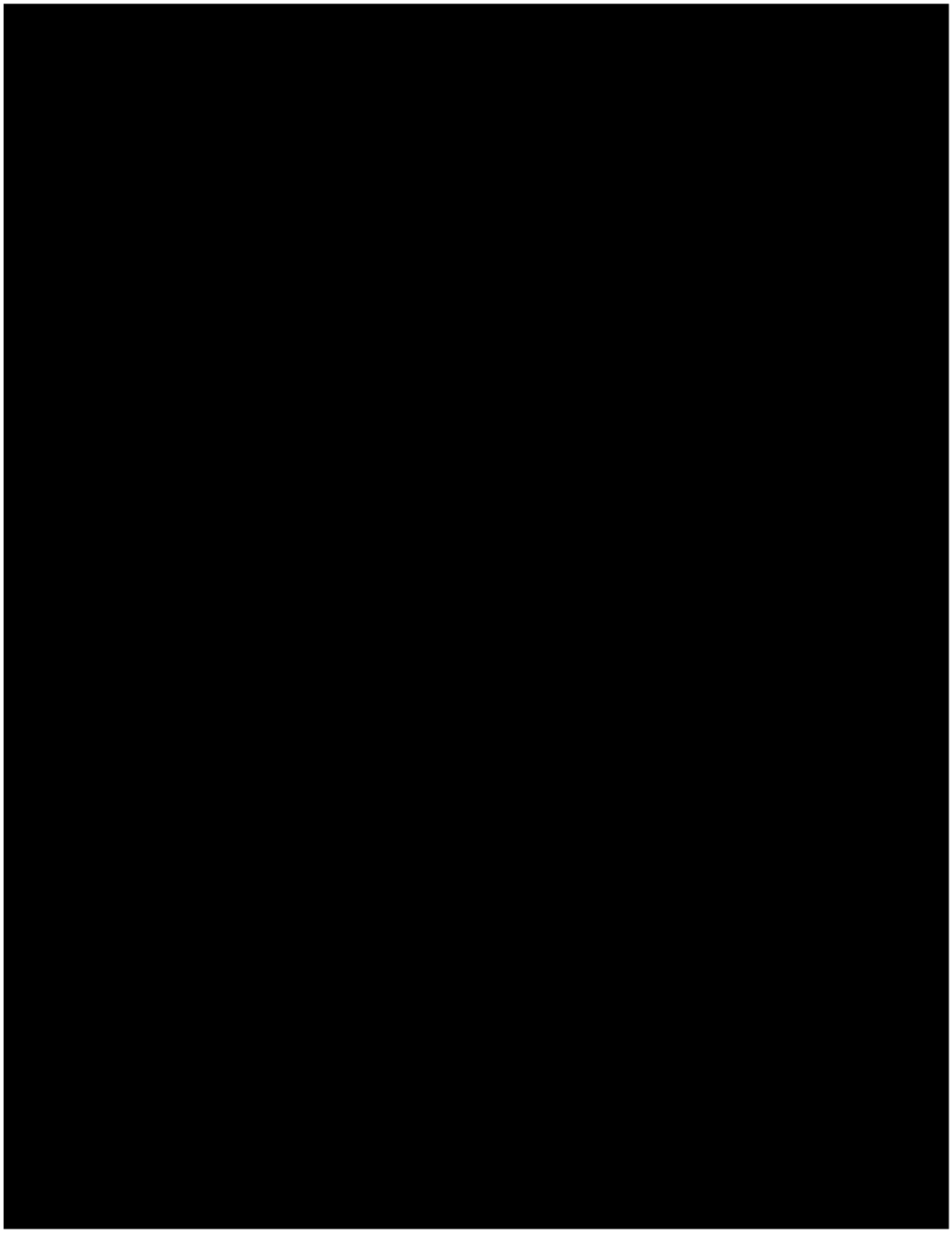
Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table A7-3.

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.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

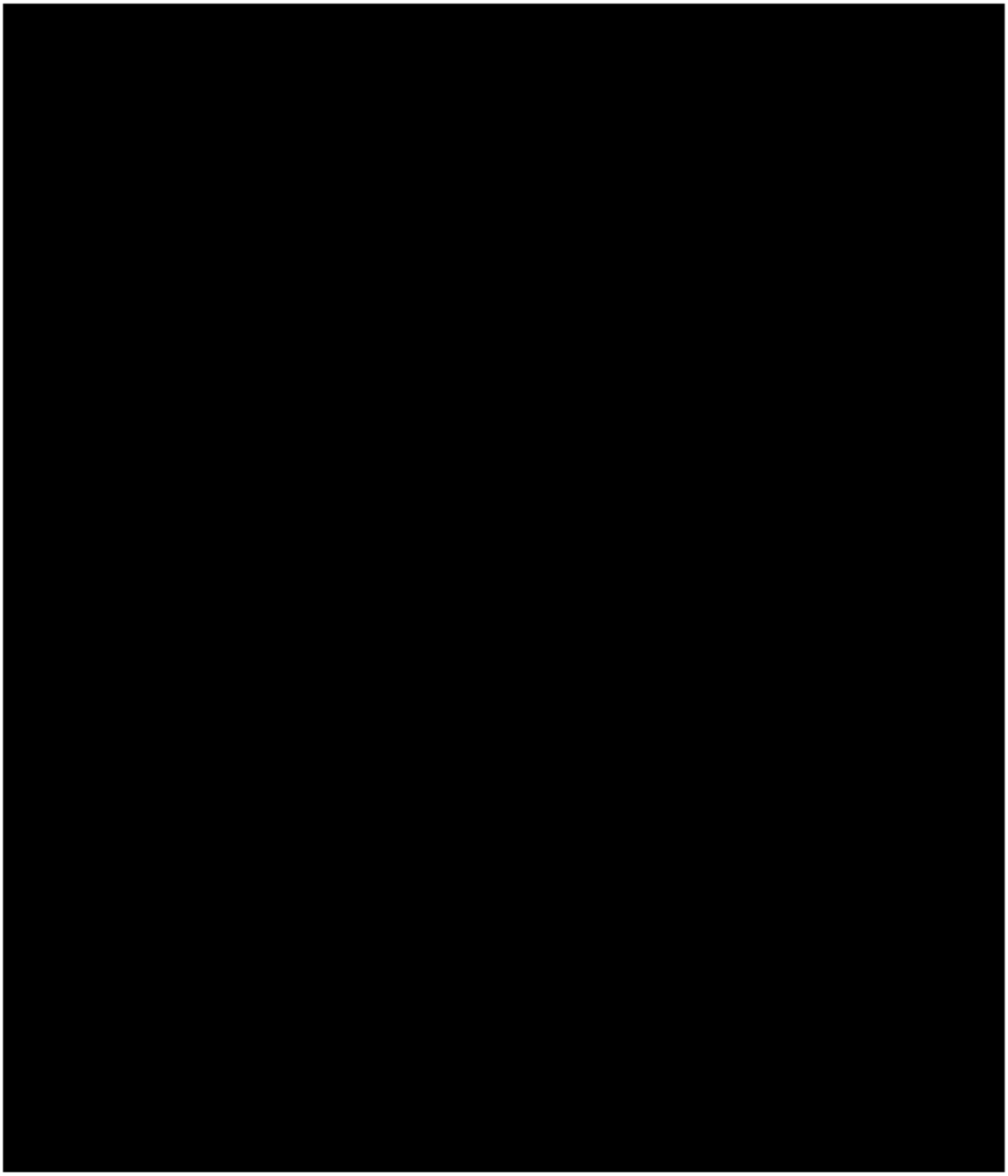


ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A7-4.

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. The patient 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.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

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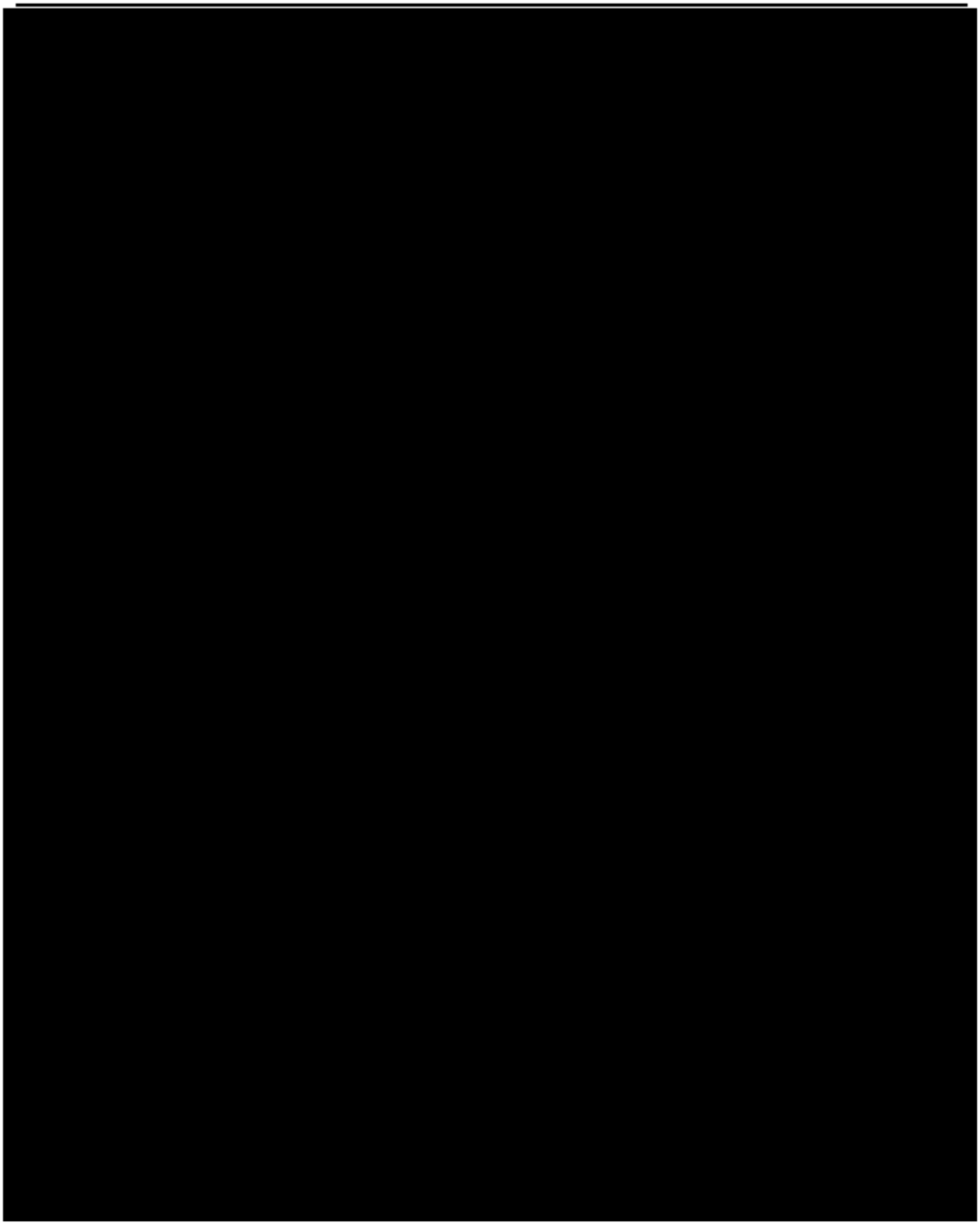
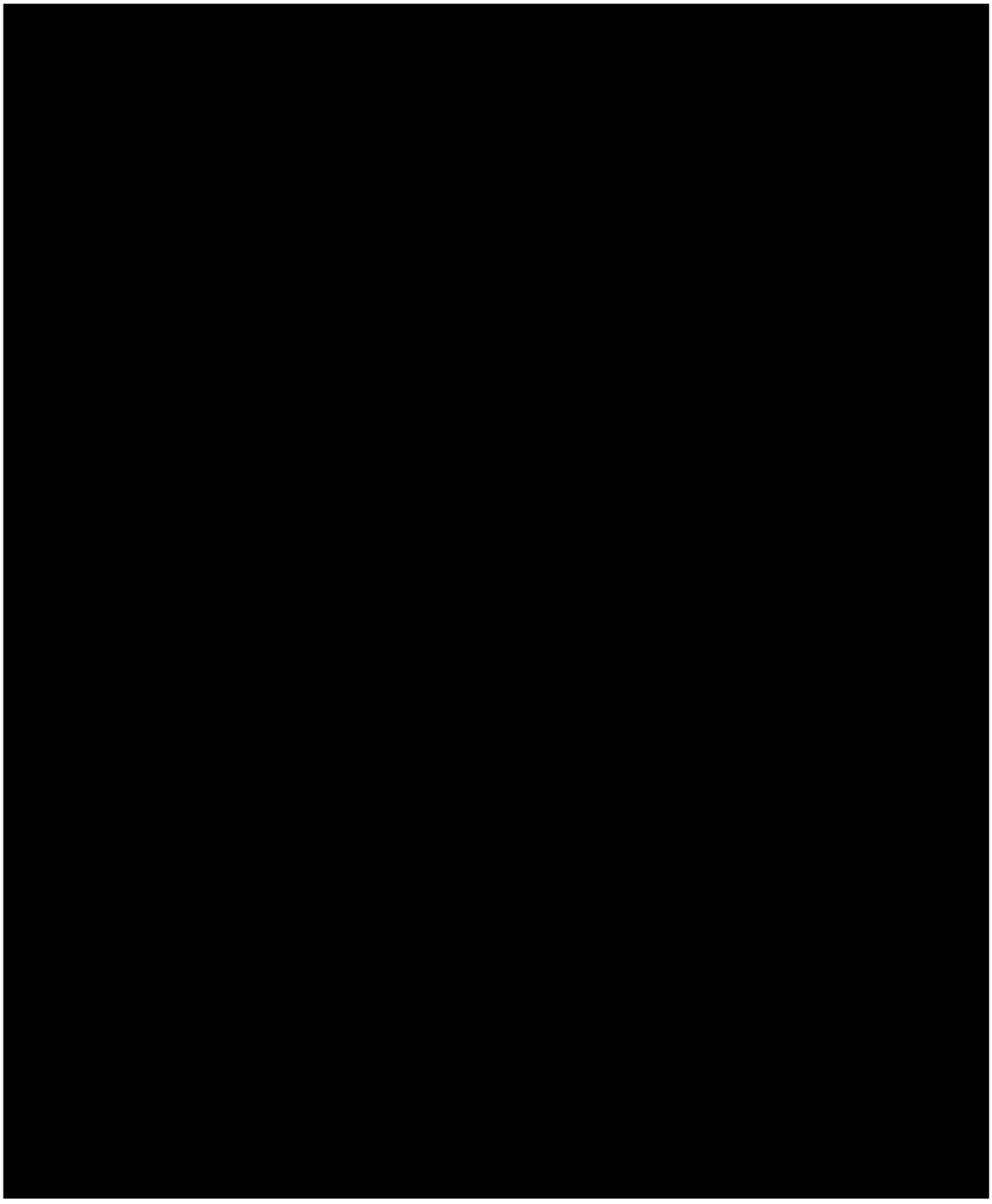
Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table A7-6.

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 or associated with pericarditis (see section on *immune-mediated* pericardial disorders below) of myositis 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.

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A7-6.

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).

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

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

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A7-6. Withhold treatment with atezolizumab and tiragolumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab or tiragolumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab or tiragolumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab and tiragolumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab or tiragolumab administration and are generally mild to moderate in severity.

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table A7-7.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and *interferon-γ* (Merad and Martin 2020). If a 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's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

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 A7-8.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

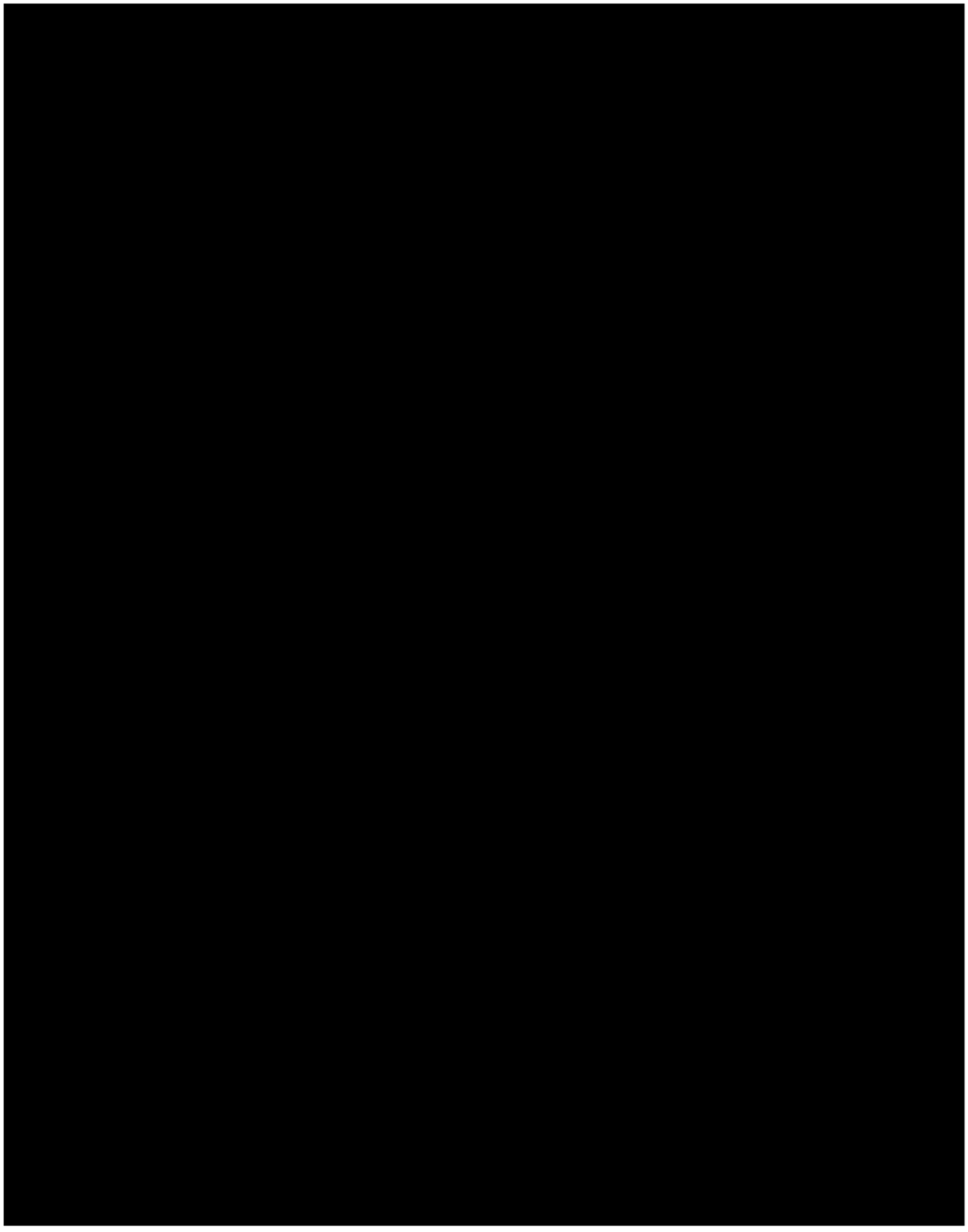
Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A7-9.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

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 A7-10, with specific guidelines for myelitis provided in Table A7-11.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

Table A7-10 Management Guidelines for Neurologic Disorders (cont.)

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.

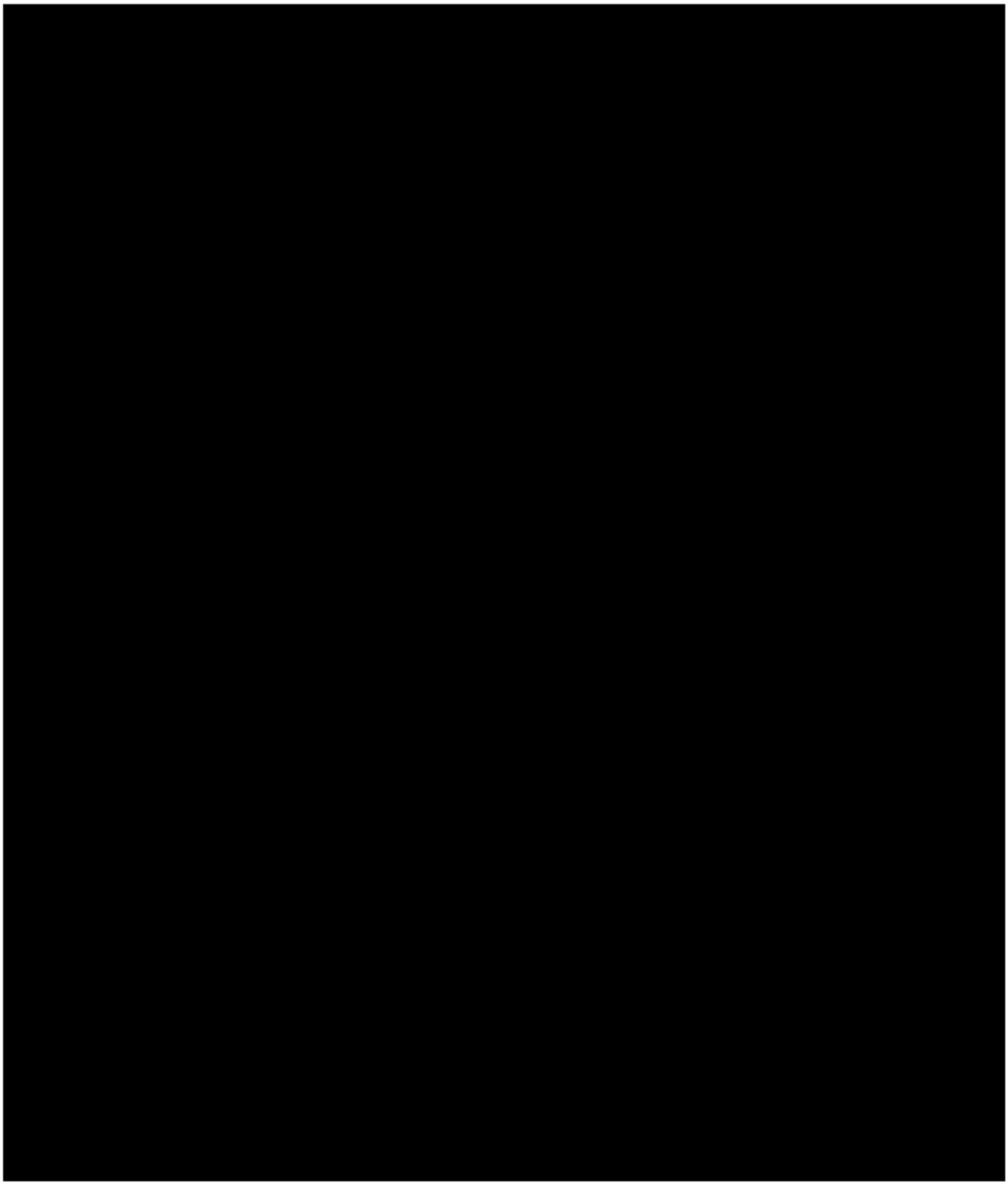
All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A7-12.

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 non-steroidal 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 A7-13.

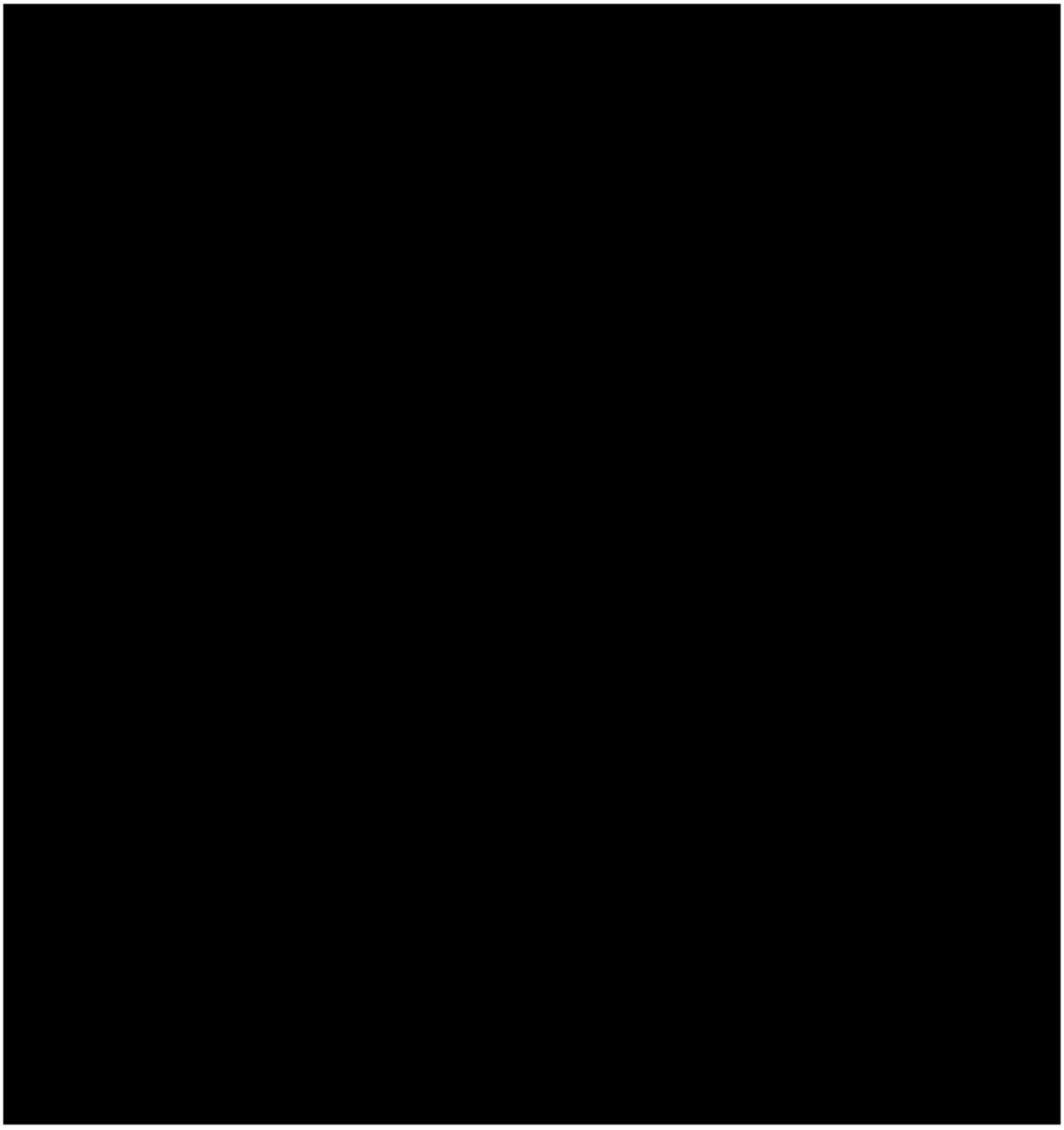


IMMUNE-MEDIATED MYOSITIS

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

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A7-14.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events



Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

[redacted]

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100 \times 10^9$/L (100,000/μL)
  - ANC $<1.0 \times 10^9$/L (<1000/μL)
- Fasting triglycerides >2.992 mmol/L (>265 mg/dL) and/or fibrinogen <1.5 g/L (<150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table A7-15.

Appendix 7: Guidelines for Management of Atezolizumab- and Tiragolumab-Specific Adverse Events

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Appendix 8
Placeholder for Future Arm

The Atezo Monotherapy Arm has been removed since the treatment has been removed from the study. Appendix 8 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 9
Study Details Specific to Atezo+Tira Arm

TABLE OF CONTENTS

A9–1 BACKGROUND ON ATEZO+TIRA ARM

A9–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death–1 (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 enhances the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and in patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union [E.U.]), non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer (in the E.U.), hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

A9–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). 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. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with 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 nonclinical and clinical studies.

A9–2 RATIONALE FOR ATEZO+TIRA ARM

A9–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and its expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including head and neck cancer, non–small cell lung cancer, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Cancer immunotherapy agents, particularly immune checkpoint inhibitors, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A9–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009). TIGIT 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 PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is

concordantly expressed with other checkpoint immune receptors such as PD-1 on the surface of T cells and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (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. It is expressed in most solid tumors, such as non–small cell lung cancer, breast cancer, head and neck cancer and melanoma, as well as in hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence activated cell-sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Guillerey at al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating $CD4^+$ T cells and in 50%–80% of tumor-infiltrating $CD8^+$ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, the data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A9–2.3 COMBINATION TREATMENT WITH ANTI–PD-L1 AND ANTI–TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti–PD-L1/PD-1 are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed effector function of chronically stimulated $CD8^+$ T cells and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, in patients, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including head and neck cancer.

A9–2.3.1 Clinical Studies of Tiragolumab as a Single Agent or in Combination with Atezolizumab

Tiragolumab is currently under investigation in two ongoing clinical studies (GO30103 and GO40290) in patients with solid tumors and in one clinical study (GO41036) in patients with hematological malignancies.

A9–2.3.1.1 Study GO30103

Study GO30103 is a first-in-human, Phase I, open-label, multicenter, global, dose escalation and dose expansion study. It was designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia portion of the study) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including head and neck squamous cell carcinoma, urothelial cancer, renal cell cancer, non–small cell lung cancer, esophageal cancer, colorectal cancer, gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the clinical cutoff date of 2 December 2020, [redacted] patients were enrolled in Study GO30103. Forty-two patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and [redacted] patients were enrolled in the Phase Ib portion to receive tiragolumab in combination with atezolizumab. The latter group included [redacted] patients who crossed over from the Phase Ia portion of the study.

The best observed response with tiragolumab monotherapy in the Phase Ia portion was prolonged stable disease in 8 of 42 patients, with some patients, including 1 patient with colorectal cancer, experiencing a decrease in tumor size.

In the Phase Ib portion, complete response was observed in [redacted] patients at tiragolumab dose levels of [redacted] and [redacted] in combination with [redacted]. Partial response was observed in [redacted] patients at tiragolumab dose levels of [redacted] and [redacted] in combination with [redacted], including [redacted] patients who crossed over from the Phase Ia portion at the [redacted] Stable disease was observed in [redacted] patients at [redacted]

[redacted]

[redacted]

A9–2.3.1.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in previously untreated patients with locally advanced unresectable or metastatic PD-L1–positive non–small cell lung cancer (defined as a tumor proportion score [TPS] ≥ 1%).

Appendix 9: Study Details Specific to Atezo + Tira Arm

As of the primary clinical cutoff date of 30 June 2019, 135 patients with a PD-L1 TPS ≥1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). As of the primary analysis, 47.8% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment in the ITT population. In the TPS ≥50% population, 65.5% of patients in the tiragolumab plus atezolizumab group versus 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

In all randomized patients, the combination of tiragolumab plus atezolizumab improved the co-primary endpoints of investigator-assessed objective response rate (ORR) and progression-free survival (PFS) compared with placebo plus atezolizumab, with median follow-up of 5.9 months. The ORR for tiragolumab plus atezolizumab was 31.3% (95% confidence interval [CI]: 19.5 to 43.2) compared with placebo plus atezolizumab that was 16.2% (95% CI: 6.7% to 25.7%). Investigator-assessed median PFS for tiragolumab plus atezolizumab was 5.4 months (95% CI: 4.2 months to not reached) compared 3.6 months (95% CI: 2.7 to 4.4 months), with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.37 to 0.90) with placebo plus atezolizumab. Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group relative to the placebo plus atezolizumab group (unstratified HR: 0.33; 95% CI: 0.15 to 0.72; median PFS: not reached vs. 3.9 months, respectively).

As of 2 December 2020, 67 safety-evaluable patients in the tiragolumab plus atezolizumab group in Study GO40290 had been treated with a median of eight doses of tiragolumab and atezolizumab (range: 1–38) for a median of 5.0 months (range: 0.03–26.0). In the placebo plus atezolizumab group, 68 safety-evaluable patients had been treated with a median of five doses of placebo and atezolizumab (range: 1–37) for a median of 2.8 months (range: 0.03–26.3).

As of 2 December 2020, 135 safety-evaluable patients had been administered either tiragolumab (600 mg; the recommended Phase II/III dose) in combination with atezolizumab or placebo in combination with atezolizumab. The safety profile of tiragolumab plus atezolizumab was similar to that of placebo plus atezolizumab for all grades of adverse events (98.5% vs. 97.1%), Grade ≥3 adverse events (53.7% vs. 50.0%), serious adverse events (47.8% vs. 39.7%), and adverse events leading to treatment discontinuation (13.4% vs. 11.8%). Adverse events of special interest were reported in 58.2% of patients in the tiragolumab plus atezolizumab group and in 32.4% of patients in the placebo plus atezolizumab group. One death attributed to Epstein-Barr virus reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in this study that was considered by the investigator to be related to the study drugs.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure *for* additional details on all ongoing and planned clinical studies.

A9–2.4 BENEFIT–RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications, including SCCHN, support a favorable benefit–risk profile for tiragolumab. Because of the reinvigoration of an anti-tumor immune response by immune-modulating radiotherapy and the potential synergism with immune-checkpoint inhibitor treatment, the potentially synergistic mechanisms of action of atezolizumab and tiragolumab, as well as their manageable and tolerable safety profiles (see Section A9-2.4), combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with SCCHN.

To evaluate overlapping toxicities of the experimental treatments in the neoadjuvant setting (refer to Section 3.1.3 for details), a minimum of 6 patients in the Atezo + Tira arm must complete a safety evaluation before additional patients can be enrolled in this arm.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.3.

A9–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + TIRA ARM

A9–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab.

A9–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle).

[redacted]

[redacted]

[redacted]

Refer to the Tiragolumab Investigator's Brochure for additional details.

A9–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA ARM

A9–4.1 TREATMENT IN ATEZO+TIRA ARM

A9–4.1.1 Formulation, Packaging, and Handling

A9–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a 60-mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of atezolizumab, refer to the pharmacy manual and the Atezolizumab Investigator's Brochure.

A9–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor as a 60-mg/mL concentrate for solution for infusion.

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

A9–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus tiragolumab (Atezo+Tira) arm will receive treatment for two cycles (6 weeks) as outlined in Table A9-1 until surgery or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A9-1 Treatment Regimen for Atezo+Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo = atezolizumab; Tira = tiragolumab.

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.6. No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

A9–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A9-2.

Table A9-2 Administration of First and Second Atezolizumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities. • Patients should be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experiences an IRR with the first infusion, premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • 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 the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.

eCRF = electronic Case Report Form; IRR = infusion-related reaction

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Table A9-4 and Appendix 7.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A9-5.1.4.2. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A9–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a postinfusion observation period as described in Table A9-3.

Administration of tiragolumab 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 5. Tiragolumab infusions will be administered according to the instructions outlined in Table A9-3.

Table A9-3 Administration of First and Second Tiragolumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over [redacted] minutes. • After the infusion of tiragolumab, the patient begins a [redacted]-minute observation period. • Record vital signs on the eCRF every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient experiences an IRR with the first infusion, premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over [redacted] minutes if the previous infusion was tolerated without an IRR or [redacted] minutes if the patient experienced an IRR with the previous infusion. • Patients should be observed for [redacted] minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR or for [redacted] minutes after completion of the tiragolumab infusion if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded on the eCRF every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) for tiragolumab are provided in Table A9-4 and Appendix 7.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A9-5.1.4.2. Tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A9–4.2 CONCOMITANT THERAPY FOR ATEZO+TIRA ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A9–4.2.1 Permitted Therapy for Atezo + Tira Arm

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

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

  Live, attenuated vaccines are not permitted (see Section A9-4.2.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

  Other use of corticosteroids may be permitted. The Medical Monitor is available to advise as needed.
- Local therapy (e.g., surgery other than removal of primary tumor and metastatic lymph nodes and not SCCHN specific)

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies 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; refer to Appendix 5 for details).

A9–4.2.2 Cautionary Therapy for Atezo + Tira Arm

A9–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. 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 7 for details).

A9–4.2.2.2 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) may be used during the study at the discretion of the investigator.

A9–4.2.2.3 Prohibited Therapy for Atezo + Tira Arm

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment until surgery, or if earlier, until disease progression is documented and the patient has discontinued study treatment
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and/or tiragolumab, and for 5 months after the final dose of atezolizumab and/or tiragolumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) within 4 weeks or 5 drug-elimination half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and/or tiragolumab

A9–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+TIRA ARM

Contraception requirements for men and women in the Atezo+Tira arm are outlined below:

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

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 90 days after the final dose of tiragolumab. Women must refrain from breastfeeding and donating eggs during this same period of time.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

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

- 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 or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab. Men must refrain from donating sperm during this same period.

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

A9–5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA ARM

A9–5.1 SAFETY PLAN FOR ATEZO+TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A9-5.1.1, A9-5.1.2, and A9-5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A9-5.1.1 and Appendix 7.

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. Because of the potential for overlapping toxicities for atezolizumab and tiragolumab, special caution will be taken by performing a planned safety evaluation phase for patients randomized to this arm (see Section 3.1.3).

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. Adverse events will be reported as described in Sections 5.2– 5.6.

A9–5.1.1 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 HLH. Refer to Appendix 7 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A9–5.1.2 Risks Associated with Tiragolumab

Infusion-related reactions and [redacted] are an identified risk for tiragolumab. [redacted] While 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 the Tiragolumab Investigator's Brochure for details on nonclinical and clinical safety assessments.

A9–5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine-release may occur. IRRs have been seen in some patients receiving tiragolumab as a single agent or in combination with atezolizumab. The events have been Grades 1 and 2 in severity and have included symptoms of pyrexia, chills, nausea, and hypertension. Other clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

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. Subsequent infusions and observation times may be shortened only if the initial dose administration is well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section A9-4.1.2 for detailed guidance on administration of tiragolumab in this study. Please see Appendix 5 for guidance on anaphylaxis precautions in Table A9-4 and Appendix 7 for guidance on the management of IRRs.

[redacted]

A9–5.1.2.3 Immune-Mediated Adverse Events

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

Clinical experience with therapeutics 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, endocrinopathy, 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. Please see Section 4.1.2 for details.

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A9-5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for suspected immune-mediated adverse events are provided in Appendix 7.

[redacted]

A9–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential 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. [redacted]

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune CPIs to date has been incorporated into the design and safety management plan (see Appendix 7) 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 CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section 4.1.2), patients with active infection (including, but not limited to, HIV, HBV, HCV, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section 4.1.2).

A9–5.1.4 Management of Patients Who Experience Specific Adverse Events in the Atezo+Tira Arm

A9–5.1.4.1 Dose Modifications

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

A9–5.1.4.2 Treatment Interruptions for Toxicities

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed, if warranted. In the neoadjuvant setting, the study treatment is limited to a presurgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets the criteria for interrupting/withholding atezolizumab and/or tiragolumab, atezolizumab and tiragolumab should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should be considered only if the benefit–risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, atezolizumab should also be withheld or discontinued.

A9–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A9-4 and Appendix 7.

For cases in which management guidelines are not covered in Appendix 7, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A9-4 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo+Tira Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs and CRS are provided in Appendix 7. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, and systemic immune activation	• Guidelines for management of these events are provided in Appendix 7.

Atezo=atezolizumab; CRS=cytokine release syndrome; GI=gastrointestinal; IRR=infusion-related reaction; Tira=tiragolumab.

A9–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+TIRA ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the Atezo+Tira arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

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

- [redacted]

A9–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+TIRA ARM

A9–5.3.1 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 or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab. 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 e-mailing the form using the fax number or e-mail 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A9–5.3.2 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 or within 90 days after the final dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail 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 the 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male 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.

A9–5.3.3 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 embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A9–5.3.4 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 5.2.2).

A9–6 SCHEDULE OF ACTIVITES FOR ATEZO+TIRA ARM

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-Day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 (+2 days)	Week 6 and/or ≤7 days to surgery	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Atezolizumab administration	Section A9-4.1.2		x	x						
Tiragolumab administration			x	x						
Molecular profile of SCCHN	Section 4.5.2		Whenever updated information becomes available							
Weight	Section 4.5.3		x [e]	x [e]	x		x	x	x	x
Complete physical examination							x			
Limited physical examination			x [e]	x [e]	x			x	x	x
Vital signs	Section 4.5.4		x	x	x		x	x	x	x
12-Lead ECG	Section 4.5.5		x [e]	x [e]			x	Perform as clinically indicated.		
ECOG PS	Appendix 3		x [e]	x [e]	x		x	x	x	x

A9-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-Day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Surgery	Section 4.5.7					x				
Tumor response assessments	Section 4.5.6				x					
Disease status assessments							x[f]	x	x	x
Concomitant medications	Section 4.4		x	x	x		x	x		
Adverse events [g]	Appendix 7		x	x	x		x	x		
Clavien-Dindo assessment	Appendix 2						x			
Hematology	Section 4.5.11.1		x[h]	x[h]	x		x	x	x	x
Chemistry			x[h]	x[h]	x		x	x	x	x
Lipid panel					x		x	Perform as clinically indicated.		

A9-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-Day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤ 7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤ 7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Coagulation: INR and aPTT	Section 4.5.11.1		x [h]	x [h]	x			Perform as clinically indicated.		
TSH, free T3 (or total T3), and free T4			x [h]		x		x	Perform as clinically indicated.		
C-reactive protein			x [h]	x [h]	x		x	Perform as clinically indicated.		
Pregnancy test [i]			x [h]	x [h]	x		x	x		
Urinalysis			Perform as clinically indicated.							
Serum autoantibody sample *j*			Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
[redacted]										

A9-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-Day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Blood and plasma [redacted]	Section 4.5.11.2		Refer to Section A9-7.							
Resected tissue						x				
Tumor biopsy (optional) [k]			x							

[redacted] approx. = approximately; Atezo = atezolizumab; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; PS = Performance Status; Q3M = every 3 months; Q6M = every 6 months; SCCHN = squamous cell carcinoma of the head and neck; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; Tira = tiragolumab; TSH = thyroid-stimulating hormone.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for an end of treatment visit 3–6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. For patients who progress or have loss of clinical benefit, the visit at which response assessment show progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit.

A9-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

[c] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first follow-up visit 3 months after surgery, and patients who do not proceed to surgery will have their first follow-up visit 3 months after the final dose of study treatment. Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months 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 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 only. For an experimental arm in which all patients discontinue treatment and pass the safety follow-up window, as well as approximately 80% of patients discontinue from the study *or all patients have been followed up for at least 2 years, whichever occurs first*, the Sponsor may conclude the arm *(all remaining patients in that arm will be discontinued from the study)*.

[d] Refer to Sections 3.1.2 and 3.1.4 for surgery time window.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] *The disease status assessments at treatment completion or early discontinuation visit ([redacted] should include a mandatory CT scan or MRI (see Section 4.5.6.2).*

[g] After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, 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 or until initiation of new systemic anti-cancer therapy, whichever occurs first. 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). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* 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.

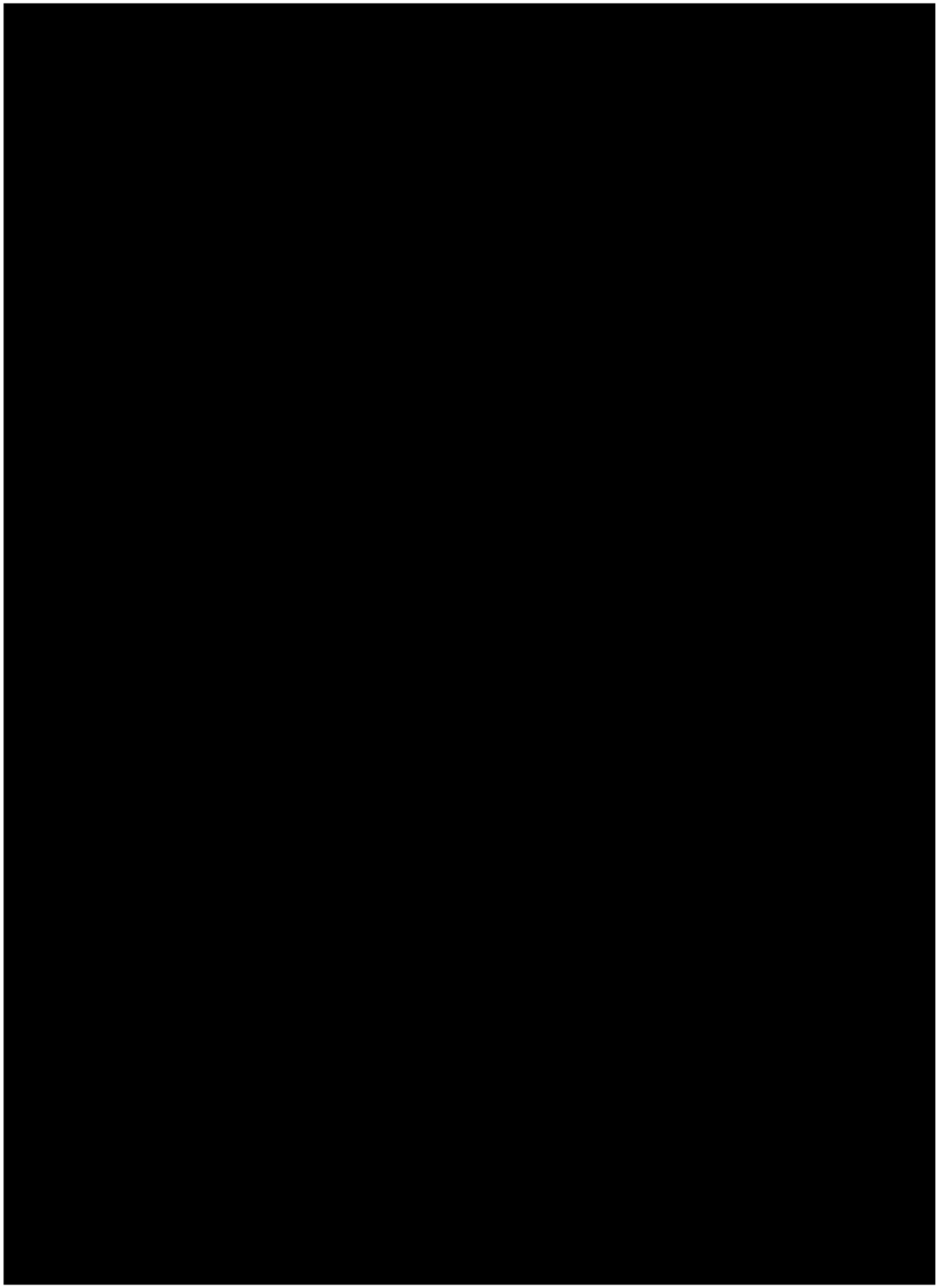
[h] Laboratory tests must be performed within 96 hours prior to Day 1 of each cycle during the treatment period. If screening laboratory assessments are performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[i] Urine or serum pregnancy tests will be performed at specified subsequent visits and at *the* 6 month *follow-up* . If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] *Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.*

[k] Performed only for patients who have signed the Optional Tumor Sample Informed Consent to participate.

Appendix 9: Study Details Specific to Atezo + Tira Arm



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Appendix 10
Placeholder for Future Arm

The Atezo + Tira + iSBRT Arm has been removed since the treatment has been removed from the study. Appendix 10 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 11
Study Details Specific to Atezo+Tira+CP Arm

TABLE OF CONTENTS

A11–1 BACKGROUND ON ATEZO+TIRA+CP ARM

A11–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death–1 (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 enhances the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and in patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma (in the European Union [E.U.]), non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer (in the E.U.), hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

A11–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ monoclonal antibody that binds to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). 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. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with 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 nonclinical and clinical studies.

A11–1.3 BACKGROUND ON CARBOPLATIN AND PACLITAXEL IN SCCHN

In locally advanced SCCHN, cisplatin and 5-fluorouracil (PF) used in the induction chemotherapy was the first regimen shown to provide organ preservation (Department of Veterans Affairs Laryngeal Cancer Study Group et al. 1991). In several randomized clinical studies, PF was compared with PF in combination with docetaxel (Vermoken et al. 2007; Posner et al. 2007; Lorch et al. 2011) or paclitaxel (Hitt et al. 2005). In these studies, the combination of a taxane with PF (TPF) improved overall survival (OS) as well as progression-free survival (PFS). In addition, induction therapy with TPF yielded similar complete response rates and even higher partial response rates, ranging from 8% to 17% and from 59% to 72%, respectively. Furthermore, with the addition of concurrent radiochemotherapy (CRT) after induction therapy with TPF demonstrated high rates of locoregional control (Hitt et al. 2005; Lefebvre et al. 2013). Therefore, TPF has become the accepted standard induction chemotherapy regimen for patients with SCCHN who are at high risk of distant metastatic spread.

Several groups have demonstrated that a less aggressive induction chemotherapy with carboplatin and paclitaxel (CP) provides complete response and partial response rates similar to TPF, ranging from 8% to 33% and from 50% to 85%, respectively (Posner et al. 2007; Lorch et al. 2011) reported Grade 3 and 4 events of neutropenia that ranged between 76% and 83% in patients receiving TPF, several trials reported the incidence of neutropenia ranging between 21% and 36% in patients receiving CP (Salama et al. 2008; Kies et al. 2010, 2011; Airoldi et al. 2011; Semaru et al. 2011; Ready et al. 2012; Vlacich et al. 2012). Furthermore, PFS and OS were consistently between 60% and 80%. Importantly, in many of these prospective series, patients tolerated CP and subsequent concurrent CRT with minimal additional toxicity. In contrast, in the TAX323 and TAX324 studies (Posner et al. 2007; Lorch et al. 2011), Grade 3 and 4 events of neutropenia were reported that ranged between 76% and 83% in patients receiving TPF, and several trials reported neutropenia between 21% and 36% in patients receiving CP (Salama et al. 2008; Kies et al. 2010, 2011; Airoldi et al. 2011; Semaru et al. 2011; Ready et al. 2012; Vlacich et al. 2012).

Thus, CP appears to be an effective induction chemotherapy regimen for SCCHN, providing similar efficacy with a slightly more favorable safety profile compared with that of TPF. In a retrospective single-institution analysis of 143 patients with locally advanced non-metastatic SCCHN, clinical outcomes of patients treated with either TPF (n=53) or CP (n=90) induction chemotherapy followed by concurrent CRT were compared. Patients receiving CP had similar rates of complete response (14.4% for CT vs. 9.4% for TPF), partial response (68.9% for CP vs. 75.5% for TPF), stable disease (8.9% for CP vs. 5.7% for TPF), and progressive disease (4.4% for CP vs. 5.7% for TPF) relative to patients treated with TPF. TPF induction chemotherapy was associated with

worse renal toxicity resulting in treatment delays relative to CP, in contrast with administration of CP once a week for 6 weeks that was associated with a greater number of neutropenia events.

In summary, CP demonstrated a potentially more favorable toxicity profile while having a similar to slightly increased hematologic toxicity and similar efficacy compared with that of TPF in the neoadjuvant induction therapy setting.

A11–2 RATIONALE FOR ATEZO+TIRA+CP ARM

A11–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses by binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and its expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including head and neck cancer, NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Cancer immunotherapy agents, particularly immune checkpoint inhibitors, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A11–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009). TIGIT 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 PVR) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated in the tumor microenvironment in many human tumors, is concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (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. It is expressed in most solid tumors, such as head and neck cancer, NSCLC, breast cancer, and melanoma, as well as in hematologic tumors, such as multiple myeloma and non-Hodgkin lymphoma. Fluorescence activated cell-sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey at al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating $CD4^+$ T cells and in 50%–80% of tumor-infiltrating $CD8^+$ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, the data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A11–2.3 COMBINATION TREATMENT WITH ANTI–PD-L1 AND ANTI-TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti–PD-L1/PD-1 are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated $CD8^+$ T cells

and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, in patients, has been shown to enhance may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including head and neck cancer.

A11–2.4 COMBINED INHIBITION OF THE PD-L1 AND TIGIT PATHWAYS PLUS CHEMOTHERAPY

The addition of PD-L1 and PD-1 checkpoint inhibitors to standard platinum-based chemotherapy demonstrated encouraging anti-tumor activity and acceptable safety in early Phase I and II studies (Giaccone et al. 2015; Langer et al. 2016; Rizvi et al. 2016). In multiple large randomized Phase III trials in different advanced solid tumors, including MK-3475-189 (KEYNOTE-189), MK-3475-407 (KEYNOTE-407), GO29436 (IMpower150), and GO29537 (IMpower130), the addition of PD-L1 and PD-1 checkpoint inhibitors to standard chemotherapy led to significantly longer OS and PFS in patients compared with chemotherapy alone (Gandhi et al. 2018; Horn et al. 2018; Paz-Ares et al. 2018; Schmid et al. 2018). Notably, 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 disease-free survival (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 the Phase I GO30103 and Phase II CITYSCAPE studies 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 under evaluation in other indications to develop more effective treatment options for patients in need.

A11–2.5 CLINICAL STUDIES OF TIRAGOLUMAB AS A SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies (GO30103 and GO40290) in patients with solid tumors and in one clinical study (GO40136) in patients with hematological malignancies.

A11–2.5.1 Study GO30103

Study GO30103 is a first-in-human, Phase I, open-label, multicenter, global, dose escalation and dose expansion study. It was designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (in Phase Ia of the study) and in combination with atezolizumab (in Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including head and neck squamous cell carcinoma, urothelial cancer, renal cell cancer, NSCLC, esophageal cancer, colorectal cancer, gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the clinical cutoff date of 2 December 2020, [redacted] patients were enrolled in Study GO30103. Forty-two patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and [redacted] patients were enrolled in the Phase Ib portion to receive tiragolumab in combination with atezolizumab. The latter group included [redacted] patients who crossed over from the Phase Ia portion of the study.

The best observed response with tiragolumab monotherapy in the Phase Ia portion was prolonged stable disease in [redacted] patients, with some patients, including [redacted] patient with colorectal cancer, experiencing a decrease in tumor size.

In the Phase Ib portion, a complete response was observed in [redacted] patients at tiragolumab dose levels of [redacted] and [redacted] in combination with [redacted]. Partial response was observed in [redacted] patients at tiragolumab dose levels of [redacted] and [redacted] in combination with [redacted], including 2 patients who crossed over from the Phase Ia portion at the [redacted] dose level. Stable disease was observed in [redacted] patients at tiragolumab dose levels of [redacted] in combination with [redacted], including [redacted] patients who crossed over from the Phase Ia portion

of the study [redacted]

[redacted]

[redacted]

[redacted]

A11–2.5.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in previously untreated patients with locally advanced unresectable or metastatic PD-L1–positive NSCLC (defined as a TPS ≥ 1%).

As of the primary clinical cutoff date of 30 June 2019, 135 patients with a PD-L1 TPS ≥ 1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n = 67) or placebo plus atezolizumab (n = 68). As of the primary analysis, 47.8% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment in the ITT population. In the TPS ≥ 50% population, 65.5% of patients in the tiragolumab plus atezolizumab group versus 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

In all randomized patients, the combination of tiragolumab plus atezolizumab improved the co-primary endpoints of investigator-assessed objective response rate (ORR) and PFS compared with placebo plus atezolizumab, with median follow-up of 5.9 months. ORR for tiragolumab plus atezolizumab was 31.3% (95% confidence interval [CI]: 19.5 to 43.2) compared with placebo plus atezolizumab that was 16.2% (95% CI: 6.7% to 25.7%). Investigator-assessed median PFS for tiragolumab plus atezolizumab was 5.4 months (95% CI: 4.2 to not reached) compared 3.6 months (95% CI: 2.7 to 4.4), with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.37 to 0.90) with placebo plus atezolizumab. Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group relative to the placebo plus atezolizumab group (unstratified HR: 0.33; 95% CI: 0.15 to 0.72; median PFS: not reached vs. 3.9 months, respectively).

As of 2 December 2020, 67 safety-evaluable patients in the tiragolumab plus atezolizumab group in Study GO40290 had been treated with a median of eight doses of tiragolumab and atezolizumab (range: 1–38) for a median of 5.0 months (range: 0.03–26.0). In the placebo plus atezolizumab group, 68 safety-evaluable patients had been treated with a median of five doses of placebo and atezolizumab (range: 1–37) for a median of 2.8 months (range: 0.03–26.3).

As of 2 December 2020 a total of 135 safety-evaluable patients had been treated with either tiragolumab (600 mg; the recommended Phase II/III dose) in combination with atezolizumab or placebo in combination with atezolizumab. The safety profile of tiragolumab in combination with atezolizumab was similar to that of placebo plus atezolizumab for all grades of adverse events (98.5% vs. 97.1%), Grade ≥ 3 adverse events (53.7% vs. 50.0%), serious adverse events (47.8% vs. 39.7%), and adverse events leading to treatment discontinuation (13.4% vs. 11.8%). Adverse events of

special interest were reported in 58.2% of patients in the tiragolumab plus atezolizumab group and in 32.4% of patients in the placebo plus atezolizumab group. One death attributed to Epstein-Barr virus reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in this study that was considered by the investigator to be related to the study drugs.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure *for* additional details on all ongoing and planned clinical studies.

A11–2.6 CLINICAL STUDIES OF ATEZOLIZUMAB AND/OR TIRAGOLUMAB IN COMBINATION WITH CHEMOTHERAPY

In multiple, large, randomized, Phase III trials of advanced solid tumors, the addition of anti–PD-L1/PD-1 to standard chemotherapy has improved OS and PFS for patients compared with chemotherapy alone. These trials studied the addition of anti–PD-1 to pemetrexed and platinum-based chemotherapy in non-squamous NSCLC (Gandhi et al. 2018) and to carboplatin and paclitaxel or nab-paclitaxel in squamous NSCLC (Paz-Ares et al. 2018). These trials also investigated the addition of anti–PD-L1 treatment to carboplatin and etoposide in extensive stage small-cell lung cancer (Horn et al. 2018) and to nab-paclitaxel in triple-negative breast cancer (Schmid et al. 2018). As a result of these trials, anti–PD-L1/PD-1 treatment in combination with chemotherapies have been approved by the U.S. Food and Drug Administration and European Medicines Agency for patients with advanced cancer.

The safety profiles resulting from combining anti–PD-L1/PD-1 and chemotherapy have generally been consistent with the known toxic effects of each agent as observed in multiple clinical trials of advanced solid tumors (Gandhi et al. 2018; Horn et al. 2018; Paz-Ares et al. 2018; Schmid et al. 2018). Given the similarities in mechanism of action between tiragolumab and atezolizumab, it is anticipated that the safety profile of tiragolumab administered in combination with atezolizumab and chemotherapy may be consistent with the immune-related toxicities of the combined anti-TIGIT and anti–PD-L1 and the toxicities of the individual chemotherapy agents.

There are several ongoing studies testing the combination of atezolizumab with or without tiragolumab in combination with cisplatin or carboplatin plus paclitaxel.

A11–2.6.1 Study GO29436 (IMpower150)

In the IMpower150 study (G029436), the combination of atezolizumab and bevacizumab with carboplatin and paclitaxel (ABCP) significantly increased PFS and OS in patients with metastatic, non-squamous NSCLC who had not previously received chemotherapy compared with bevacizumab plus carboplatin and paclitaxel (BCP) (8.3 vs. 6.8 months; HR for disease progression or death: 0.62; 95% CI: 0.52 to 0.74; $p<0.001$).
The incidence of Grade 1 or 2 treatment-related adverse events was 35.9% in the ABCP group and 45.4% in the BCP group. The most common Grade 3 or 4 treatment-related adverse events were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension. Treatment-related deaths were reported for 11 patients (2.8%) in the ABCP group and 9 patients (2.3%) in the BCP group:

Five deaths with ABCP were due to pulmonary hemorrhage or hemoptysis. Of the 5 patients who died, 4 patients had potentially high-risk features (e.g., tumor infiltration of great vessels or cavitation).

Treatment-related serious adverse events were noted in 25.4% of the patients in the ABCP group and in 19.3% of those in the BCP group. Furthermore, 77.4% of the immune-related adverse events that occurred in the ABCP group were of Grade 1 or 2 severity and none were Grade 5. The most common immune-related adverse events were rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis (Socinski et al. 2018).

A11–2.6.2 Study YO42138

In addition, the combination of atezolizumab plus tiragolumab and cisplatin plus Paclitaxel is being tested in a randomized, double-blind, placebo-controlled study (NCT04540211) in treatment-naive patients with unresectable, locally advanced esophageal squamous cell carcinoma. In this study, no new safety signals have been detected to date and an independent Data Monitoring Committee recently recommended to continue enrollment after a routine ongoing benefit–risk assessment.

A11–2.6.3 Study YO39609

The combination of atezolizumab plus tiragolumab and cisplatin plus 5-FU is being tested in patients with metastatic esophageal cancer in the Phase Ib study YO39609. To date, the safety profile of the combination of atezolizumab plus tiragolumab and cisplatin plus 5-FU has been consistent with the safety profile of the respective single agents and no new safety signals have been observed.

A11–2.6.4 Additional Clinical Studies

There are ongoing Phase Ib, II, and III studies (GO41717, GO41767, GO41854, GO42501, and BO42592) 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.

A11–2.7 BENEFIT–RISK ASSESSMENT

To date, there is evidence of improved radiographic and pathological responses when combining checkpoint inhibitor agents with chemotherapy in the neoadjuvant setting compared with chemotherapy alone (Provencio et al. 2019; 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 checkpoint inhibitor treatment, with and without platinum-based chemotherapy in NSCLC. The preliminary safety and efficacy data from the ongoing studies of tiragolumab or in combination with atezolizumab across different solid tumor indications, including SCCHN as well as the preclinical and clinical data available for the combination of atezolizumab with tiragolumab plus a platinum- or taxane-based chemotherapy, support a favorable benefit–risk profile for this combination. Furthermore, this study includes stringent eligibility criteria, baseline measurements, and comprehensive 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.

The favorable benefit–risk profile, the potential for PD-L1 and TIGIT as a target for therapeutic intervention in SCCHN, and the significant unmet medical need in this indication are key reasons for the implementation of this study arm.

To evaluate overlapping toxicities of the experimental treatments in the neoadjuvant setting (refer to Section A11-5.1.3 for details), a minimum of 6 patients in the Atezo + Tira + CP arm must complete a safety evaluation before additional patients can be enrolled in this arm (refer to Section 3.1.3 for details).

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.3.

A11–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + TIRA + CP ARM

A11–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab.

A11–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle).

[redacted]

Refer to the Tiragolumab Investigator's Brochure for additional details.

A11–3.3 RATIONALE FOR PACLITAXEL DOSE AND SCHEDULE

Paclitaxel will be administered at the approved dose of 175 mg/m^2 IV Q3W (175 mg/m^2 on Day 1 of each 21-day cycle).

A11–3.4 RATIONALE FOR CARBOPLATIN DOSE AND SCHEDULE

Carboplatin will be administered by IV infusion at the approved dose of AUC 5 mg/mL/min Q3W (area under the concentration–time curve [AUC] 5 on Day 1 of each 21-day cycle).

A11–4 MATERIALS AND METHODS SPECIFIC TO ATEZO+TIRA+CP ARM

A11–4.1 TREATMENT IN ATEZO+TIRA+CP ARM

A11–4.1.1 Formulation, Packaging, and Handling

A11–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a 60-mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of atezolizumab, refer to the pharmacy manual and the Atezolizumab Investigator's Brochure.

A11–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor as a 60-mg/mL concentrate for solution for infusion.

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

A11–4.1.1.3 Carboplatin

For information on the formulation, packaging, and handling of carboplatin, refer to the local prescribing information.

A11–4.1.1.4 Paclitaxel

For information on the formulation, packaging, and handling of paclitaxel, refer to the local prescribing information.

A11–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus tiragolumab plus carboplatin plus paclitaxel arm (Atezo + Tira + CP) arm will receive treatment for two cycles (6 weeks) as outlined in Table A11-1 until surgery or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A11-1 Treatment Regimen for Atezo + Tira + CP Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle • Paclitaxel 175 mg/m^2 on Day 1 of each cycle • Carboplatin AUC 5 mg/mL/min (calculated using the Calvert formula for dosing) IV on Day 1 of each cycle

Atezo = atezolizumab; AUC = area under the concentration–time curve; CP = carboplatin and paclitaxel; Tira = tiragolumab.

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.6. No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

A11–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A11-2.

Table A11-2 Administration of First and Second Atezolizumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities. • Patients should be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experiences an IRR with the first infusion, premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • 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 the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.

eCRF = electronic Case Report Form; IRR = infusion-related reaction

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Table A11-7 and Appendix 7.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A11-5.2. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A11–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a postinfusion observation period as described in Table A11-3.

Administration of tiragolumab 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 5. Tiragolumab infusions will be administered according to the instructions outlined in Table A11-3.

Table A11-3 Administration of First and Second Tiragolumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over [redacted] minutes. • After the infusion of tiragolumab, the patient begins a [redacted]-minute observation period. • Record vital signs on the eCRF every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient experiences an IRR with the first infusion, premedication with antihistamines, antipyretic *medications*, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over [redacted] minutes if the previous infusion was tolerated without an IRR or [redacted] minutes if the patient experienced an IRR with the previous infusion. • Patients should be observed for [redacted] minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR or for [redacted] minutes after completion of the tiragolumab infusion if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded on the eCRF every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

Guidelines for medical management of IRRs for tiragolumab are provided in Table A11-7 and Appendix 7.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A11-5.2. Tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures)

after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A11–4.1.2.3 Paclitaxel

Paclitaxel will be administered by IV infusion at a dose of 175 mg/m^2 over approximately 180 minutes on Day 1 of each cycle. On Day 1 of Cycle 1, paclitaxel will be administered at least [redacted] minutes after completion of the tiragolumab infusion to allow for observation after tiragolumab administration.

The interval between subsequent tiragolumab infusions will be [redacted] minutes if the previous atezolizumab and tiragolumab infusion was tolerated without an IRR or at least [redacted] minutes if the patient experienced an IRR with the previous atezolizumab or tiragolumab infusion.

Patients should receive antiemetic medications and IV hydration according to institutional standards and the manufacturer's instructions for paclitaxel and carboplatin.

Paclitaxel can cause severe allergic reaction because of the drug carrier. Therefore, patients should receive premedication prior to each paclitaxel dose, including corticosteroids, in alignment with local guidelines. The recommended premedication for paclitaxel is listed in Table A11-4.

Table A11-4 Recommended Premedication for Paclitaxel

Premedication	Dose and Route of Administration	Timing
Dexamethasone	20 mg PO	12 and 6 hours before paclitaxel (or per standard of care at treating institution)
Diphenhydramine (or equivalent)	50 mg IV	30–60 minutes before paclitaxel
Cimetidine (or ranitidine) (or equivalent)	300 mg (or 50 mg) IV (or equivalent)	30–60 minutes before paclitaxel

PO = orally.

Because of the immunomodulatory effects of corticosteroids, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

All medications must be recorded on the appropriate Concomitant Medications eCRF.

Paclitaxel will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for paclitaxel dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A11-5.2. Paclitaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A11–4.1.2.4 Carboplatin

Carboplatin will be administered by IV infusion to achieve an initial target AUC of 5 mg/mL/min (calculating using the Calvert formula for dosing) over 30–60 minutes on Day 1 of each cycle after the completion of paclitaxel infusion.

Patients should receive antiemetic medications and IV hydration according to institutional standards and manufacturer's instructions for paclitaxel and carboplatin.

All medications must be recorded on the appropriate Concomitant Medications eCRF. Carboplatin will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for carboplatin dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A11-5.2. Carboplatin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) after consultation with the Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A11–4.2 CONCOMITANT THERAPY FOR ATEZO+TIRA+CP ARM

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 study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A11–4.2.1 Permitted Therapy for Atezo+Tira+CP Arm

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

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

- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A11-4.2.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

  Other use of corticosteroids may be permitted. The Medical Monitor is available to advise as needed.
- Local therapy (e.g., surgery other than removal of primary tumor and metastatic lymph nodes and not SCCHN specific)

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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies 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; refer to Appendix 7 for details).

A11–4.2.2 Cautionary Therapy for Atezo+Tira+CP Arm

A11–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. 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 7 for details).

A11–4.2.2.2 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 A11-4.2.2.4) may be used during the study at the discretion of the investigator.

A11–4.2.2.3 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

The chemotherapeutic agents used in this study are associated with potential drug–drug interactions. The metabolism of paclitaxel is catalyzed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4.

Caution should be exercised when paclitaxel is concomitantly administered with known strong, moderate, or weak inhibitors, and/or inducers of CYP2C8 (e.g., gemfibrozil, clopidogrel, deferasirox, teriflunomide, trimethoprim) and (e.g., rifampin), respectively, and strong, moderate, or weak inhibitors and/or inducers of CYP3A4 (e.g., boceprevir, cobicistat, danoprevir, ritonavir, elvitegravir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir, aprepitant, ciprofloxacin, conivaptan, crizontinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil, chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, ticagrelor) and (e.g., apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone, armodafinil, modafinil, rufinamide) respectively, drug–drug interactions with any medication that is metabolized by or strongly inhibits or induces these enzymes. Therefore, the medications listed above should be avoided when paclitaxel is being administered. If use of one of these medications is necessary, the benefits and risks should be discussed.

A11–4.2.2.4 Prohibited Therapy for Atezo+Tira+CP Arm

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment until surgery, or if earlier, until disease progression is documented and the patient has discontinued study treatment
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and/or tiragolumab, and for 5 months after the final dose of atezolizumab and/or tiragolumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) within 4 weeks or 5 drug-elimination half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and/or tiragolumab

A11–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO+TIRA+CP ARM

A11–4.3.1 Contraception Requirements for Atezo+Tira+CP Arm

Contraception requirements for men and women in the Atezo+Tira+CP arm are outlined below:

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

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

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- 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 or 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 carboplatin or paclitaxel. Men must refrain from donating sperm during this same period.

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

A11–5 ASSESSMENT OF SAFETY FOR ATEZO+TIRA+CP ARM

A11–5.1 SAFETY PLAN FOR ATEZO+TIRA+CP ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies and the prescribing information for carboplatin and paclitaxel. The anticipated important safety risks are outlined below (see Sections A11–5.1.1, A11–5.1.2, and A11–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A11-5.1.1 and Appendix 7).

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. Because of the potential for overlapping toxicities for atezolizumab and tiragolumab, special caution will be taken by performing a planned safety evaluation phase for patients randomized to this arm (see Section 3.1.3).

Administration of atezolizumab and tiragolumab 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. Adverse events will be reported as described in Sections 5.2–5.6.

A11–5.1.1 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 HLH. Refer to Appendix 7 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A11–5.1.2 Risks Associated with Tiragolumab

Infusion-related reactions [redacted] are an identified risk for tiragolumab. [redacted] While 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 the Tiragolumab Investigator's Brochure for details on nonclinical and clinical safety assessments.

A11–5.1.2.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic monoclonal antibody and targets immune cells, IRRs associated with hypersensitivity reactions and/or target-mediated cytokine-release may occur. IRRs have been seen in some patients receiving tiragolumab as a single agent or in combination with atezolizumab. The events have been Grades 1 and 2 in severity and have included symptoms of pyrexia, chills, nausea, and hypertension. Other clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

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. Subsequent infusions and observation times may be shortened only if the initial dose administration is well tolerated. All infusions of tiragolumab will be administered in an appropriate medical setting.

Refer to Section A11-4.1.2 for detailed guidance on administration of tiragolumab in this study. Please see Appendix 5 for guidance on anaphylaxis precautions and Appendix 7 for guidance on the management of IRRs.

[redacted]

A11–5.1.2.3 Immune-Mediated Adverse Events

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

Clinical experience with therapeutics 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, endocrinopathy, 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. Please see Section 4.1.2 for details.

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A11-5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for suspected immune-mediated adverse events are provided in Appendix 7.

[redacted]

[redacted]

[redacted]

[redacted]

A11–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential 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. [redacted]

[redacted]

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune CPIs to date has been incorporated into the design and safety management plan (see Appendix 7) 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 CIT will also be excluded from participation in this study. Owing to the risks of active viral infection and viral reactivation (see Section 4.1.2), patients with active infection (including, but not limited to, HIV, HBV, HCV, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Section 4.1.2).

A11–5.1.4 Risks Associated with Paclitaxel

Paclitaxel is known to cause bone marrow suppression (e.g., myelosuppression, anemia and thrombocytopenia), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, peripheral neuropathy, hypersensitivity reactions, arthralgia or myalgia, injection site reactions, alopecia, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, and other ECG abnormalities. Patients will be monitored for paclitaxel-related adverse events. For more details regarding the safety profile of paclitaxel, refer to the paclitaxel prescribing information.

A11–5.1.5 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression, including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events

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

A11–5.1.6 Risks Associated with Combination Use of Atezolizumab and Tiragolumab and Carboplatin/Paclitaxel

The risk of overlapping toxicities between tiragolumab/atezolizumab and carboplatin and paclitaxel 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 carboplatin and paclitaxel (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tiragolumab and/or atezolizumab.

A11–5.2 MANAGEMENT OF PATIENTS WHO EXPERIENCE SPECIFIC ADVERSE EVENTS IN THE ATEZO+TIRA+CP ARM

At the start of each cycle, ANC must be ≥1500/μL and the platelet count must be ≥100,000/μL. Treatment may be delayed for up to 3 weeks 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 American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2015; Pfister et al. 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 A11-3). 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 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.

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, complete 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.

A11–5.2.1 Dose Modification

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

For management of drug-related toxicities, the dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Table A11-5.

Table A11-5 Dose Reductions for Paclitaxel and Carboplatin

	Initial Dose	Reduced by One Dose Level	Reduced by Two Dose Levels
Paclitaxel	175 mg/m^2	135 mg/m^2	90 mg/m^2
Carboplatin	AUC 5	AUC 3.75	AUC 2.5

AUC=area under the concentration–time curve.

If the dose of one chemotherapy drug is reduced because of a toxicity considered to be solely related to that drug, there is no need to reduce the dose of the other chemotherapy drug.

The dose of paclitaxel may be reduced to 135 mg/m^2 (one dose level), 90 mg/m^2 (two dose levels), e.g., for the management of study drug–related toxicities (i.e., from 175 mg/m^2 to 135 mg/m^2 and then from 135 mg/m^2 to 90 mg/m^2).

The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times, e.g., for management of study drug–related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min).

If further dose reduction is indicated after reduction by two dose levels, the patient must discontinue both paclitaxel and carboplatin but may continue treatment with atezolizumab and tiragolumab at the investigator's discretion. After dose reduction, the dose will not be escalated during subsequent administrations.

A11–5.2.2 Treatment Interruptions for Toxicities

A11–5.2.2.1 Atezolizumab and Tiragolumab

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed, if warranted. In the neoadjuvant setting, the study treatment is limited to a presurgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets the criteria for interrupting/withholding atezolizumab and/or tiragolumab, atezolizumab and tiragolumab should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should be considered only if the benefit–risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, atezolizumab should also be withheld or discontinued.

A11–5.2.2.2 Carboplatin and Paclitaxel

Paclitaxel and/or carboplatin treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Section A11-5.2). If paclitaxel or cisplatin have been withheld for > 3 weeks because of toxicity, the patient should be discontinued from both chemotherapy agents. However, paclitaxel or cisplatin can be resumed after being withheld for > 3 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit.

If one or more study treatments is interrupted, subsequent cycles should be restarted such that the study treatment infusions remain synchronized.

However, if it is anticipated that chemotherapy will be delayed by ≥ 2 weeks, then atezolizumab and tiragolumab should be given without the chemotherapy if there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy.

If atezolizumab is discontinued, tiragolumab should also be discontinued, but paclitaxel and carboplatin may be continued if the patient is likely to derive clinical benefit, as determined by the investigator. If paclitaxel or carboplatin is discontinued, the other drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

A11–5.3 MANAGEMENT GUIDELINES FOR ADVERSE EVENTS

Guidelines for the management of patients who experience specific adverse events are provided in Table A11-6 and Appendix 7.

For cases in which management guidelines are not covered in Appendix 7, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

For adverse events associated with paclitaxel or carboplatin that are not listed in Table A11-6 or Table A11-7, refer to guidelines in the applicable local prescribing information (if available) or Summary of Product Characteristics. For cases in which management guidelines are not covered in the protocol or prescribing information, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table A11-6 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira + CP Arm

Events	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs and CRS for atezolizumab and tiragolumab are provided in Appendix 7. • Guidelines for management of IRRs for paclitaxel and carboplatin are provided in Table A11-7. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Pulmonary, hepatic, gastrointestinal, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, and systemic immune activation	• Guidelines for management of these events are provided in Table A11-7 and Appendix 7.

Atezo = atezolizumab; CP = carboplatin and paclitaxel; CRS = cytokine release syndrome; GI = gastrointestinal; IRR = infusion-related reaction.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event

Event	Action to Be Taken
Infusion-related reactions, anaphylaxis, and hypersensitivity reactions	• For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Infusion-related reaction to chemotherapy, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
Infusion-related reaction to chemotherapy, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medications, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic medications and monitor closely for IRRs.
Infusion-related reaction to chemotherapy, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact Medical Monitor. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Diarrhea or colitis, Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin and reduce dose of paclitaxel and carboplatin by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]
Diarrhea or colitis, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume paclitaxel and *carboplatin and reduce dose of paclitaxel and carboplatin* by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]
Hematologic toxicity	
Febrile neutropenia	
Grade 3 or 4	• Withhold atezolizumab, tiragolumab, paclitaxel, and carboplatin. • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) ≤3 weeks after event onset, resume atezolizumab and tiragolumab. Resume paclitaxel and carboplatin with the dose reduced by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a] • If fever resolves and ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) >3 weeks and ≤6 weeks after event onset, resume atezolizumab and tiragolumab. [b] Permanently discontinue paclitaxel and carboplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Hematologic toxicity (cont.)	
Nadir during prior cycle, excluding febrile neutropenia	
ANC $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab, tiragolumab, paclitaxel, and carboplatin.
ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count $< 100 \times 10^9$/L (100,000/μL)	• Continue atezolizumab and tiragolumab. Withhold paclitaxel and carboplatin. • If ANC improves to $\geq 1.5 \times 10^9$/L (1500/μL) and/or Platelet count improves to $\geq 100 \times 10^9$/L (100,000/μL) ≤3 weeks after event onset resume paclitaxel and carboplatin at one dose level reduced. • If not, permanently discontinue paclitaxel and carboplatin. [a]
Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Continue atezolizumab and tiragolumab. Withhold paclitaxel and carboplatin. • If Platelet count improves to $\geq 100 \times 10^9$/L (100,000/μL) ≤3 weeks after event onset resume paclitaxel and carboplatin at one dose level reduced. • If not, permanently discontinue paclitaxel and carboplatin. [a]
Platelet count $< 50 \times 10^9$/L (50,000/μL) with Grade ≥2 bleeding, regardless of ANC	• Continue atezolizumab and tiragolumab. Withhold paclitaxel and carboplatin. • If platelet count improves to $\geq 100 \times 10^9$/L (100,000/μL) ≤3 weeks after event onset resume carboplatin at two dose levels reduced and paclitaxel at one dose level reduced. • If not, permanently discontinue paclitaxel and carboplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Dermatologic events (other than injection-site reaction)	
Dermatologic event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Dermatologic event, Grade 2 or 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin with dose reduced by one level. [b] • If event persists, permanently discontinue paclitaxel and carboplatin. [a]
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Permanently discontinue paclitaxel and carboplatin. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Pulmonary events	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Pulmonary event, Grade 2 or 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin with the dose reduced by one level. If not, permanently discontinue paclitaxel and carboplatin. [a] • For recurrent events, treat as a Grade 4 event.
Pulmonary event, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Permanently discontinue paclitaxel and carboplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Neurologic *disorders*	
Immune-mediated neuropathy, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel with dose reduced by one level. If not, permanently discontinue carboplatin and paclitaxel. [a]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • *Permanently discontinue paclitaxel and carboplatin.* [a]
Myasthenia gravis or Guillain-Barré syndrome, all grades	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated myelitis, Grade 1	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated myelitis, Grade 2	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated myelitis, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated meningoencephalitis, all grades	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.* [a]
Chemotherapy-related neurotoxicity, Grade 2	• Continue atezolizumab and tiragolumab. • Withhold carboplatin and paclitaxel. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel with the dose reduced by one level. If not, permanently discontinue carboplatin and paclitaxel. [a]
Chemotherapy-related neurotoxicity, Grade 3 or 4	• Withhold atezolizumab, tiragolumab, carboplatin, and paclitaxel. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume atezolizumab, tiragolumab. Reduced carboplatin and paclitaxel with the dose reduced by two dose levels. If not, permanently discontinue carboplatin and paclitaxel. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken		
Hepatic events			
Hepatic event, Grade 1	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.		
Hepatic event, Grade 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin for hepatic event other than Grade 2 elevation of AST, ALT, or ALP. • If chemotherapy is withheld and event resolves to Grade 1 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin. If not, permanently discontinue paclitaxel and carboplatin. [a]		
Hepatic event, Grade 3	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]		
Hepatic event, Grade 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Permanently discontinue paclitaxel and carboplatin. [a]		
Dose Modifications for Paclitaxel Note: Recommendations for paclitaxel dose adjustments are extrapolated from dose adjustments for patients with hepatic impairment at baseline.			
SGOT (AST) Levels		Bilirubin Levels	Paclitaxel Reduction from Starting Dose
<10 × upper limit of normal	and	≤1.25 × upper limit of normal	No change
<10 × upper limit of normal	and	1.26–2.0 × upper limit of normal	Reduce by one dose level.
<10 × upper limit of normal	and	2.01–5.0 × upper limit of normal	Reduce by two dose levels.
>10 × upper limit of normal	or	>5.0 × upper limit of normal	Discontinue paclitaxel [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Endocrine events	
Hypothyroidism, Grade 1 or 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Hypothyroidism, Grade 3 or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • *Resume paclitaxel and carboplatin when* symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 1	**Thyroid-stimulating hormone ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin. **Thyroid-stimulating hormone < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism.
Hyperthyroidism, Grade 2, 3, or 4	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Withhold paclitaxel and carboplatin. • *Resume paclitaxel and carboplatin when* symptoms are controlled and thyroid function is improving.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin* • *If event resolves to Grade 1 or better ≤3 weeks after event onset and patient is stable on replacement therapy, resume paclitaxel and carboplatin with the dose reduced by one level. If not, permanently discontinue paclitaxel and carboplatin.* [a]

[a] *Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.*

[b] *The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.*

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Hyperglycemia, Grade 1 or 2	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Continue paclitaxel and carboplatin.*
Hyperglycemia, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *Resume paclitaxel and carboplatin when symptoms resolve and glucose levels are stable.*
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin* • *If event resolves to Grade 1 or better ≤3 weeks after event onset and patient is stable on replacement therapy, resume paclitaxel and carboplatin with the dose reduced by one level. If not, permanently discontinue paclitaxel and carboplatin.* [a] • *For recurrent hypophysitis, treat as a Grade 4 event.*
Hypophysitis (pan-hypopituitarism), Grade 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.*
Ocular events	
Ocular event, Grade 1	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Continue paclitaxel and carboplatin.* • *If symptoms persist, treat as a Grade 2 event.*
Ocular event, Grade 2	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin with the dose reduced by one level. If not, permanently discontinue paclitaxel and carboplatin.* [a]
Ocular event, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.*

[a] *Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.*

[b] *The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.*

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	*Action to Be Taken*
Cardiovascular events	
Immune-mediated myocarditis, Grades 2–4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated pericardial disorders, Grades 2–4 (also including Grade 1 pericarditis)	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a]
Cardiac rhythm disturbances (paclitaxel only)	
Asymptomatic bradycardia	• Continue paclitaxel.
Symptomatic arrhythmia during infusion	• Stop paclitaxel infusion. • Manage arrhythmia according to standard practice. • Permanently discontinue paclitaxel.
Cardiac rhythm disturbances (paclitaxel only)	
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. • Consider epinephrine or bronchodilators if chest pain is not thought to be cardiac in nature. • Cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought. • Permanently discontinue paclitaxel.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	*Action to Be Taken*
Pancreatic events	
Amylase or lipase elevation, Grade 2	*Amylase and/or lipase >1.5–2.0 ×ULN:* • *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Continue paclitaxel and carboplatin.* *Asymptomatic with amylase and/or lipase >2.0–5.0 ×ULN:* • *Treat as a Grade 3 event.*
Amylase or lipase elevation, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a] • *For recurrent events, permanently discontinue paclitaxel and carboplatin.*
Immune-mediated pancreatitis, Grade 2 or 3	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a] • *For recurrent events, permanently discontinue paclitaxel and carboplatin.*
Immune-mediated pancreatitis, Grade 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.*
Renal events	
Renal event, Grade 1	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Continue paclitaxel and carboplatin.*
Renal event, Grade 2	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a]
Renal event, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.*

[a] *Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.*

[b] *The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.*

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Immune-mediated myositis events	
Immune-mediated myositis, Grade 1	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Continue paclitaxel and carboplatin.*
Immune-mediated myositis, Grade 2	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold paclitaxel and carboplatin.* • *If event resolves to Grade 1 or better ≤3 weeks after event onset, resume carboplatin and paclitaxel reduced by one dose level.* [b] *If not, permanently discontinue paclitaxel and carboplatin.* [a]
Immune-mediated myositis, Grade 3 or 4	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Permanently discontinue paclitaxel and carboplatin.*
Suspected hemophagocytic lymphohistiocytosis	• *Follow guidelines for atezolizumab and tiragolumab in Appendix 7.* • *Withhold all treatment and contact Medical Monitor for guidance.*
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, tiragolumab, paclitaxel, and carboplatin.
Grade 3	• Continue atezolizumab and tiragolumab. Withhold paclitaxel and carboplatin. • If event resolves to Grade 2 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin and consider reducing dose by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]
Grade 4	• Withhold atezolizumab, tiragolumab, paclitaxel, and carboplatin. • If event improves and Medical Monitor agrees that atezolizumab and tiragolumab should be continued, resume atezolizumab and tiragolumab. If not, permanently discontinue atezolizumab and tiragolumab. • If event resolves to Grade 2 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin and consider reducing dose by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

Table A11-7 Guidelines for Management of Patients Who Experience Specific Adverse Event (cont.)

Event	Action to Be Taken
Atezolizumab- and tiragolumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab and tiragolumab in Appendix 7. • Continue paclitaxel and carboplatin.
Grade 3 or 4	• Follow guidelines in Appendix 7. • Withhold paclitaxel and carboplatin. • If event resolves to Grade 2 or better ≤3 weeks after event onset, resume paclitaxel and carboplatin and consider reducing the dose by one level. [b] • If not, permanently discontinue paclitaxel and carboplatin. [a]

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. The Medical Monitor is available to advise as needed.

[b] The dose of paclitaxel and the dose of carboplatin may be reduced by up to two times, as outlined in Section A11-5.2.

A11–5.4 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO+TIRA+CP ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the Atezo+Tira arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

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

- [redacted]

A11–5.5 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO+TIRA+CP ARM

A11–5.5.1 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 or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab or within 6 months after the final dose of paclitaxel or carboplatin.

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 e-mailing the form using the fax number or e-mail 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A11–5.5.2 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 or within 90 days after the final dose of tiragolumab or within 6 months after the final dose of paclitaxel or carboplatin. 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 e-mailing the form using the fax number or e-mail 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 the 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male 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.

A11–5.5.3 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 embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A11–5.5.4 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 5.2.2).

A11–6 SCHEDULE OF ACTIVITES FOR ATEZO+TIRA+CP ARM

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-day cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Atezolizumab administration	Section A11-4.1.2		x	x						
Tiragolumab administration			x	x						
Carboplatin administration			x	x						
Paclitaxel administration			x	x						
Molecular profile of SCCHN	Section 4.5.2		Whenever updated information becomes available							
Weight			x [e]	x [e]	x		x	x	x	x
Complete physical examination							x			
Limited physical examination			x [e]	x [e]	x			x	x	x
Vital signs			x	x	x		x	x	x	x

A11-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA + CP ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
12-Lead ECG	Section 4.5.5		x [e]	x [e]			x	Perform as clinically indicated		
ECOG PS	Appendix 3		x [e]	x [e]	x		x	x	x	x
Surgery	Section 4.5.7					x				
Tumor response assessments	Section 4.5.6				x					
Disease status assessments							x *f*	x	x	x
Concomitant medications	Section 4.4		x	x	x		x	x		
Adverse events *g*	Appendix 7		x	x	x		x	x		
Clavien-Dindo assessment	Appendix 2						x			

A11-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA + CP ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-day Cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day 1 *(+2 days)*	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Hematology	Section 4.5.11.1		x [h]	x [h]	x		x	x	x	x
Chemistry			x [h]	x [h]	x		x	x	x	x
Lipid panel					x		x	Perform as clinically indicated.		
Coagulation: INR and aPTT			x [h]	x [h]	x			Perform as clinically indicated.		
TSH, free T3 (or total T3), and free T4			x [h]		x		x	Perform as clinically indicated.		
C-reactive protein			x [h]	x [h]	x		x	Perform as clinically indicated.		
Pregnancy test [i]			x [h]	x [h]	x		x	x		
Urinalysis			Perform as clinically indicated.							

A11-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA + CP ARM (cont.)

Assessment or Procedure	Protocol Section or Appendix	Screening (see Appendix 6)	Treatment Cycles (21-day cycles) [a]		Presurgery [a]	Surgery [a]	Treatment Completion or Early Discontinuation [a, b]	Follow-Up [a]		
			Cycle 1	Cycle 2				Years 1 and 2 [c]	Years 3–5 [c]	Year 6 and beyond [c]
		Days –28 to –1	Day 1 (≤7 days after randomization)	Day (+2 days)	Week 6 (and/or ≤7 days to surgery)	[redacted]	[redacted] days after surgery and prior to adjuvant SOC)	Approx. Q3M (±2 weeks)	Q6M (±4 weeks)	Once Every Year (±4 weeks)
Serum autoantibody sample *i*			Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
[redacted]										
Blood and plasma samples for biomarkers	4.5.11.2		Refer to Section A11-7.							
Resected tissue						x				
Tumor biopsy (optional) *k*			x							

[redacted] approx. = approximately; Atezo = atezolizumab; Carb = carboplatin; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; Pac = paclitaxel; [redacted] PS = Performance Status; Q3M = every 3 months; Q6M = every 6 months; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; Tira = tiragolumab; TSH = thyroid-stimulating hormone.

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

A11-6 SCHEDULE OF ACTIVITIES FOR ATEZO+TIRA+CP ARM (cont.)

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for an end of treatment visit 3–6 weeks after surgery, and patients who do not proceed to surgery will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. *For patients who progress or have loss of clinical benefit, the visit at which response assessment show progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit.*

[c] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first follow-up visit 3 months after the final dose of study treatment. 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 3 months 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 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 only. For an experimental arm in which all patients discontinue treatment and pass the safety follow-up window, as well as approximately 80% of patients discontinue from the study *or all patients have been followed up for at least 2 years, whichever occurs first*, the Sponsor may conclude the arm *(all remaining patients in that arm will be discontinued from the study)*.

[d] Refer to Sections 3.1.2 and 3.1.4 for surgery time window.

[e] Assessment may be performed within 24 hours prior to dosing during the treatment period.

[f] *The disease status assessments at treatment completion or early discontinuation visit* [redacted] *should include a mandatory CT scan or MRI (see Section 4.5.6.2).*

[g] After initiation of study treatment, all adverse events will be reported until [redacted] days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, 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 or until initiation of new systemic anti-cancer therapy, whichever occurs first. 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). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* 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.

[h] Laboratory tests must be performed within 96 hours prior to Day 1 of each cycle during the treatment period. If screening laboratory assessments are performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

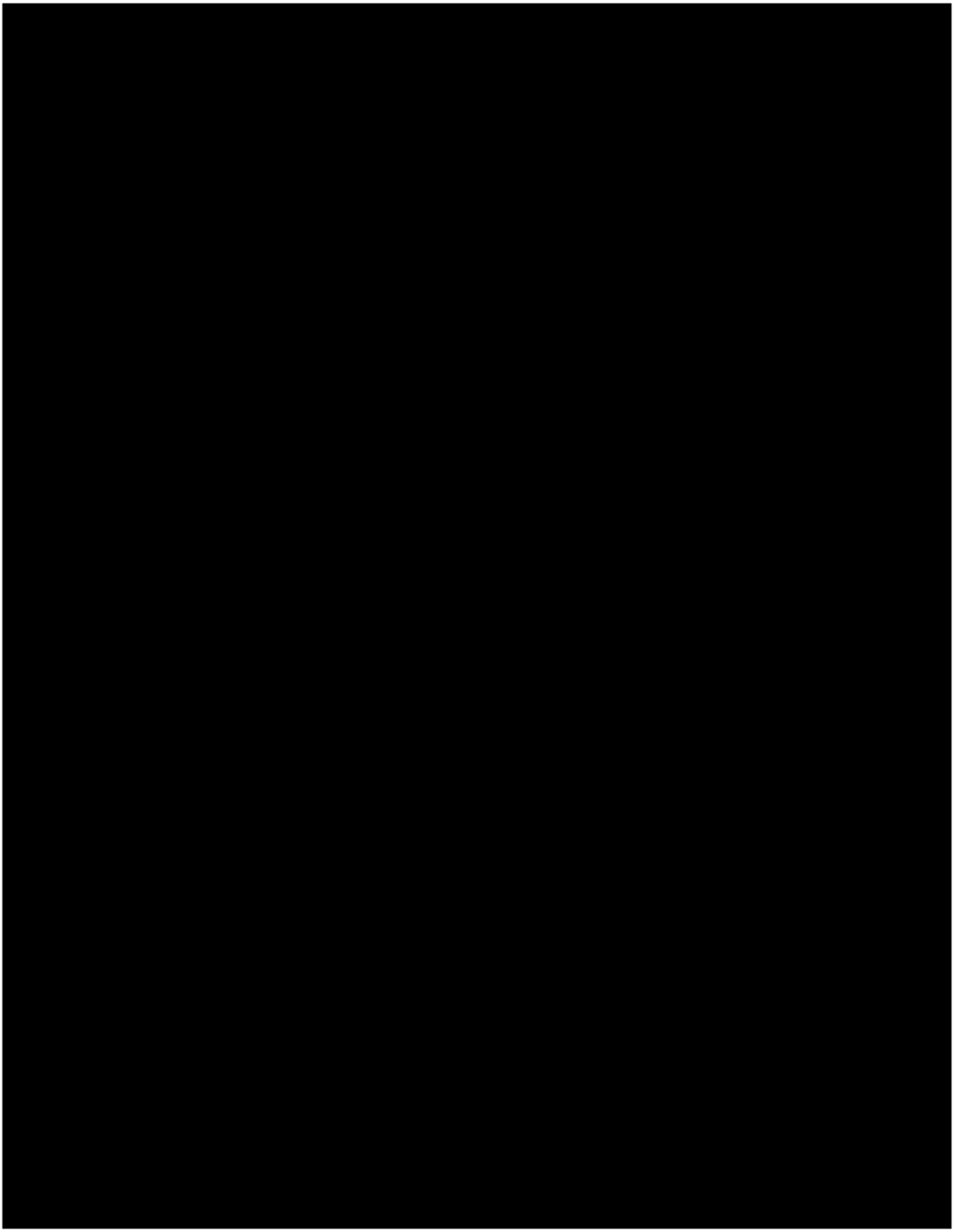
[i] Urine or serum pregnancy tests will be performed at specified subsequent visits and at *the* 6 month follow-up. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

A11-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA + CP ARM (cont.)

[j] *Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Serum samples collected for the assessment of PK, ADAs, or biomarkers at baseline on Day 1 of Cycle 1 prior to the first dose of study treatment, may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.*

[k] Performed only for patients who have signed the Optional Tumor Sample Informed Consent to participate.

Appendix 11: Study Details Specific to Atezo + Tira + CP Arm



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Appendix 12
Investigational Medicinal Product, Auxiliary Medicinal Products and Non-Investigational Medicinal Product Designations (for Use in European Economic Area)

Table A12-1 Investigational and Auxiliary Medicinal Product Designations for European Economic Area under Clinical Trials Regulation (CTR EU No 536/2014)

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Tiragolumab (RO7092284)	IMP (test product) [a]	Unauthorized	Not applicable
Paclitaxel	IMP (test product)	Authorized	No [b]
Carboplatin	IMP (test product)	Authorized	No [c]
Dexamethasone	AxMP (rescue medication)	Authorized	Yes
Diphenhydramine	AxMP (rescue medication)	Authorized	Yes
Cimetidine	AxMP (rescue medication)	Authorized	Yes
Ranitidine	AxMP (rescue medication)	Authorized	No [d]
Analgesic/antipyretic (e.g., acetaminophen)	AxMP (rescue medication)	Authorized	Yes

AxMP=Auxiliary Medicinal Product, EEA=European Economic Area; IMP=investigational medicinal product.

[a] Atezolizumab and tiragolumab are each considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab and paclitaxel are not approved for treatment of head and neck cancer.

[c] Carboplatin is indicated for treatment of head and neck cancer, but not in combination with atezolizumab, tiragolumab and paclitaxel.

[d] Ranitidine is considered to be the standard of care.

Table A12-2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area under Clinical Trials Directive (CTD 2001/20/EC)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product) [a]	Authorized	No [b]
Tiragolumab (RO7092284)	IMP (test product) [a]	Unauthorized	Not applicable
Paclitaxel	IMP (test product)	Authorized	No [b]
Carboplatin	IMP (test product)	Authorized	No [c]
Dexamethasone	NIMP (rescue medication)	Authorized	Yes
Diphenhydramine	NIMP (rescue medication)	Authorized	Yes
Cimetidine	NIMP (rescue medication)	Authorized	Yes
Ranitidine	NIMP (rescue medication)	Authorized	No [d]
Analgesic/antipyretic (e.g., acetaminophen)	NIMP (rescue medication)	Authorized	Yes

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

[a] Atezolizumab and tiragolumab are each considered to be an IMP test product as well as an IMP comparator.

[b] Atezolizumab and paclitaxel are not approved for treatment of head and neck cancer.

[c] Carboplatin is indicated for the treatment of head and neck cancer, but not in combination with atezolizumab, tiragolumab and paclitaxel.

[d] Ranitidine is considered to be the standard of care.

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