Official Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

NCT Number: NCT03452137

Document Date: Protocol Version 12: 24-February-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY AFTER DEFINITIVE LOCAL THERAPY IN PATIENTS WITH HIGH-RISK LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
PROTOCOL NUMBER:	WO40242
STUDY NAME:	IMvoke010
VERSION NUMBER:	12
TEST COMPOUND	Atezolizumab (RO5541267)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 135963 EudraCT Number: 2017-003302-40 EU CT Number: Not applicable NCT Number: 03452137
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		Associated Region-Specific Protocol		
Version	**Date Final**	**Region**	**Version**	**Date Final**
12	See electronic date stamp on final page of this document.			
11	4 November 2021			
10	22 October 2021			
9	7 January 2021			
8	16 December 2019			
7	17 December 2019	VHP	7	6 February 2019
6	10 October 2018			
5	15 June 2018			
4	1 April 2018			
3	21 February 2018			
2	3 November 2017			
1	2 October 2017			

PROTOCOL AMENDMENT, VERSION 12: RATIONALE

Protocol WO40242 has been amended to align with the Atezolizumab Investigator's Brochure [redacted] and Clinical Trials Regulation (CTR) guidelines. Changes to the protocol, along with a rationale for each change, are summarized below.

- A section describing duration of participation has been added to align with CTR requirements (Section 3.3).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 4.1.1, 4.1.2, 5.1.2.1, and Appendix 7).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.10.6).
- The list of identified risks for atezolizumab has been revised [redacted]
- [redacted]
- To address a request by [redacted] on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).
- [redacted]
- [redacted]
- The medical term "primary biliary cirrhosis" has been replaced by the term "primary biliary cholangitis" as the term "primary biliary cholangitis" is outdated in clinical practice to align with the updated preferred term in MedDRA (Appendix 7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, [redacted] to the Atezolizumab Investigator's Brochure, [redacted] (Appendix 9).

Additionally, changes have been made to comply with the EU Clinical Trial Regulation (CTR):

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Protocol Title Page, Protocol Amendment Acceptance Form, and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this

information will be provided separately to sites. The synopsis has been simplified to align with CTR and other guidelines.

- Text has been added to indicate that the HPV assay is investigational (Section 4.5.6).
- A description of the technical and organizational security measures taken to protect personal data has been added (Section 8.3).
- [redacted]
- A comprehensive list of investigational medicinal products has been added (Appendix 10).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY AFTER DEFINITIVE LOCAL THERAPY IN PATIENTS WITH HIGH-RISK LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
PROTOCOL NUMBER:	WO40242
VERSION NUMBER:	12
TEST COMPOUND	Atezolizumab (RO5541267)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY AFTER DEFINITIVE LOCAL THERAPY IN PATIENTS WITH HIGH-RISK LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
REGULATORY AGENCY IDENTIFIER NUMBERS:	EudraCT Number: 2017-003302-40 IND Number: 135963 EudraCT Number: 2017-003302-40 EU CT Number: To be determined NCT Number: 03452137

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of atezolizumab, a checkpoint inhibitor, in patients with locally advanced squamous cell carcinoma in the head and neck (SCCHN) region who have received definitive local therapy (combined modality approaches that may include chemotherapy, surgery, and/or radiotherapy). Patients who do not progress after definitive local therapy do not receive any additional therapy and the standard of care is observation; however, there remains a high risk of recurrence after 5 years. As such, there continues to be a need for additional therapies that can improve the long-term prognosis.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of atezolizumab compared with placebo as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck (SCCHN). Specific objectives and corresponding endpoints for the study are outlined in the following table.

Objectives and Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab compared with placebo	• Investigator-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by investigator, or death from any cause, whichever occurs first
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab compared with placebo	• OS after randomization, defined as the time from randomization to death from any cause • IRF-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurs first • IRF-assessed EFS and investigator-assessed EFS at 1, 2, 3, and 4 years • OS at 2, 3, and 5 years
• To evaluate clinical benefit in atezolizumab compared with placebo in terms of impact on *HR*QoL and physical functioning	• Change from baseline in physical functioning over time while receiving treatment as assessed through use of the five-item Physical Functioning subscale (Questions 1–5) of the EORTC QLQ-C30 • Change from baseline in *HR*QoL over time while receiving treatment, as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety and tolerability of atezolizumab	• Incidence and severity of adverse events, including serious adverse events, and immune-mediated adverse events, with severity determined according to NCI CTCAE v4.0
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab	• Serum concentrations of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the incidence and titers of ADAs against atezolizumab	• Incidence of ADA response to atezolizumab

ADA=anti-drug antibody; ctDNA=circulating tumor DNA; EFS=event-free survival; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; GHS=global health status; *HRQoL–Health-related quality of life;* IRF=Independent Review Facility; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS=overall survival; PRO=patient-reported outcome; QLQ-C30=Quality of Life–Core 30 Questionnaire;

QLQ-H&N35 = Quality of Life–Head and Neck, Module 35 Questionnaire; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SCCHN = squamous cell carcinoma of the head and neck; TMB = tumor mutation burden; VAS = Visual Analog Scale.

OVERALL DESIGN AND STUDY POPULATION

Study WO40242 is a global Phase III, multicenter, randomized, double-blind, placebo-controlled- study of atezolizumab as adjuvant therapy after definitive local therapy in patients with locally advanced SCCHN who are at high risk for disease recurrence or progression following definitive local therapy. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of adjuvant treatment with atezolizumab compared with placebo in patients with locally advanced SCCHN who have not progressed after receiving definitive local therapy.

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

Phase:	Phase III	**Population Type:**	Adult Patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Patients with histologically confirmed locally advanced, high risk squamous cell carcinoma of the head and neck
Interventional Model:	Parallel	**Population Age:**	≥18years
Test Compound{s}:	Atezolizumab	**Site Distribution:**	Multi-site
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	406

STUDY TREATMENT

Atezolizumab (fixed dose of 1200 mg) or placebo will be administered by IV infusion on Day 1 of each 21-day cycle for 16 cycles (or up until 1 year, whichever occurs first), or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor, whichever occurs first.

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 1 year.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as anti-therapeutic antibody (ATA)
AJCC	American Joint Committee on Cancer
C1D1	Cycle 1, Day 1
CL	clearance
COPD	chronic obstructive pulmonary disease
COVID–19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CRT	chemoradiotherapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
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
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
ESMO	European Society for Medical Oncology
Fc	fragment crystallizable
FDA	Food and Drug Administration
GHS	global health status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papillomavirus
HR	hazard ratio
IC	(tumor-infiltrating) immune cell
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
IHC	immunohistochemistry
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
M	distant metastasis
MDD	minimum detectable difference
mOS	median overall survival
MRI	magnetic resonance imaging
N	regional lymph node
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PS	Performance Status
Q3W	every 3 weeks
QLQ-C30	Quality-of-Life–Core 30 Questionnaire
QLQ-H&N35	Quality-of-Life–Head and Neck, Module 35 Questionnaire
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiation therapy
SAP	Statistical Analysis Plan

Abbreviation	Definition
SARS-CoV-2	severe acute respiratory syndrome corona virus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy for Cancer
T	primary tumor
T3	triiodothyronine
T4	thyroxine
TNF-α	tumor necrosis factor–α
ULN	upper limit of normal
VAS	Visual Analog Scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 OVERVIEW OF SCCHN

Head and neck cancers are a cause of significant morbidity and mortality, accounting for more than 550,000 cases and 380,000 deaths annually worldwide (Global Burden of Disease Cancer Collaboration 2017). Head and neck cancers are 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, and accounts for over 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 separately 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 is also a contributing factor in the development of second primary tumors within the head and neck region, esophagus, and lung in patients with SCCHN due to the field cancerization effect (Erkal et al. 2001; Slaughter et al. 1953). However, more patients are now being diagnosed with oropharyngeal cancers in their forties (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 cancers tend to be younger and 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).

Approximately one-third of patients with SCCHN present with Stage I or II (early stage) disease. Such patients are treated with either primary surgery or definitive radiation therapy (RT). The 5-year overall survival (OS) rate in patients with Stage I or II disease is between 70% and 90% (Brockstein et al. 2017). RT or surgery are equally effective treatments, and the choice of therapy is dependent upon the anatomic site, the surgical expertise, accessibility of the tumor, functional outcomes, and morbidity associated with each modality.

The majority of patients with SCCHN present with locally advanced disease (Stage III–IVB). Although these patients are treated with definitive local therapy, locally advanced disease is associated with a poor outcome with 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 survival 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).

More recent data suggest that patient outcomes have improved. The 8-year rate for OS was approximately 48% in patients with Stage III and IV carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. The 8-year rate was 70.9% relative to 30.2% for p16-positive and p16-negative patients, respectively (RTOG0129) (Nguyen et al. 2014). In the JAVELIN 100 Head & Neck trial, median OS was not reached in previously untreated patients with locally advanced SCCHN treated with standard-of-care CRT after follow-up of 16.8 months (Lee et al. 2021). Similarly, in the LUX-Head & Neck 2 trial, median OS was not estimable in patients with locoregionally advanced, unresected SCCHN who had a CR with CRT, with or without resection of residual disease after follow-up of about 22 months (Burtness et al. 2019).

For patients with recurrent or metastatic SCCHN (HPV-negative Stage IVC and HPV-positive Stage IV disease), the prognosis 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 plus 5-fluorouracil, with or without cetuximab, is usually the first-line option for fit patients (Clavel et al. 1994; Forastiere et al. 1998; Gibson et al. 2005; Vermorken et al. 2008). In the second-line and beyond refractory setting, single agents are commonly used and more recently, pembrolizumab (Chow et al. 2016; Larkins et al. 2017) and nivolumab (Ferris et al. 2016) have been approved in this setting.

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. These combined modality approaches include primary surgery followed by either postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy followed by primary surgery and/or RT or CRT, induction chemotherapy followed by RT or CRT alone, concurrent CRT without surgery, or CRT followed by salvage surgery. A number of factors impact 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. Studies have shown that combining chemotherapy with RT postoperatively reduces the risk of recurrence of disease in comparison 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 in comparison with RT alone (Bonner et al. 2006).

The current standard of care for patients with locally advanced SCCHN who are not surgical candidates includes a combination of RT (65–70 Gy in 35 fractions over

7 weeks) with concurrent cisplatin (most commonly given 100 mg/m^2 every 3 weeks [Q3W] or less commonly 40 mg/m^2 every week for the duration of RT) or concurrent weekly treatment with cetuximab and RT (Bonner et al. 2006; Pignon et al. 2009).

The use of additional/maintenance or adjuvant chemotherapy in patients who have residual disease and/or high-risk features after completion of definitive local therapy has been evaluated in several randomized trials, but with disappointing results. Suboptimal compliance with maintenance treatment may in part explain the lack of benefit, because tolerance of chemotherapy can be poor after surgery and RT (Final Report of the Head and Neck Contracts Program 1987). Despite these limitations and the lack of convincing survival benefit, patterns of failure were affected in selected studies, with a decrease in distant metastases that were consistent with a biologic effect of chemotherapy (Laramore et al. 1992).

After definitive local therapy is completed, the National Comprehensive Cancer Network (NCCN) guidelines® (Version 2; 2017) and the European Society of Medical Oncology (ESMO) guidelines (Grégoire et al. 2010) do not recommend any additional therapy for patients who have not progressed after treatment, and the current standard of care is observation to monitor patients for local recurrence and/or distant metastases. Patients treated with definitive local therapy have a 65% risk of recurrence in 5 years (Adelstein et al. 2003). There are currently no drugs approved for use after definitive local therapy and no additional adjuvant intervention has shown efficacy to date, although a number of studies are ongoing (see Table 1) (Pignon et al. 2009).

The rationale for surveillance after definitive local therapy is that early detection of either a recurrence or a second primary tumor allows for earlier treatment and may lead to better survival outcomes. However, there are no controlled prospective data demonstrating a survival benefit for any follow-up strategy to date, and despite high compliance with recommended surveillance, survival remains poor for patients who were previously treated for advanced-stage disease or who initially presented with regional disease (Agrawal et al. 2009). According to NCCN guidelines in oncology for head and neck cancers (Version 2; 2017), the general approach for surveillance is to examine patients every 1 to 3 months in the first year after treatment. In the second year, this is extended to every 2 to 4 months; in Years 3 to 5, every 4 to 8 months; and after 5 years, every 12 months.

Table 1 Completed and Ongoing Phase II/III Studies of Concurrent Chemoradiotherapy followed by Adjuvant Treatment in Patients with Locally Advanced SCCHN

Sponsor (Trial)	Sample Size (n)	Local Definitive Therapy Phase	Therapy in Adjuvant/ Maintenance Phase	Duration of Adjuvant Therapy	Primary Efficacy Endpoint	Status as of Aug. 2017
GSK (NCT00424255)	668	Lapatinib concurrent with CRT vs. placebo concurrent with CRT	Lapatinib vs. placebo	1 year	DFS	Completed (Nov. 2013) [a]
Heinrich-Heine University (NCT00791141)	80	Cetuximab in combination with RT, cisplatin, and 5-FU	Cetuximab	6 months	2-year DFS	Completed (Sept. 2013)
Boehringer Ingelheim (NCT01345669)	616	SOC CRT	Afatinib vs. placebo	1.5 years [b]	DFS	Terminated [b]
University of Chicago (NCT01111058)	160	SOC CRT	Everolimus vs. placebo	1 year	2-year tumor PFS rate	Ongoing
University of Chicago (NCT01185171)	65	CRT concurrent with gefitinib	Gefitinib	Until progression	Response rate (CR only)	Ongoing
University of Chicago (NCT02841748)	100	SOC local therapy	Pembrolizumab vs. placebo	1 year	PFS per RECIST v1.1	Ongoing
Azienda Ospedalieor Universitaria Cargeggi (NCT03051906)	69	Concurrent durvalumab, cetuximab, and RT	Durvalumab	6 months	PFS per RECIST v1.1	Ongoing
Groupe Oncologie Radiotherapie Tete et Cou (NCT02999087) [c]	688	Cisplatin + RT (fit for cisplatin), cetuximab + avelumab + RT (fit for cisplatin), cetuximab + avelumab + RT (unfit for cisplatin), and cetuximab + RT (unfit for cisplatin)	Avelumab (for cetuximab + avelumab + RT arms only); no therapy in other arms	1 year (for cetuximab + avelumab + RT arms only)	PFS per modified RECIST v1.1	Ongoing
Merck (KEYNOTE-412 [NCT03040999])	780	Pembrolizumab + cisplatin + RT vs. placebo + cisplatin + RT	Pembrolizumab vs. placebo	1 year	EFS per RECIST v1.1	Ongoing
Pfizer (Javelin Head and Neck100 [NCT02952586])	640	Avelumab + SOC CRT (cisplatin + RT) vs. placebo + SOC CRT (cisplatin + RT)	Avelumab vs. placebo	1 year	PFS per modified RECIST v1.1	Ongoing

5-FU = 5-fluorouracil; CR = complete response; CRT = chemoradiotherapy; DFS = disease-free survival; EFS = event-free survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RT = radiation therapy; SCCHN = squamous cell carcinoma of the head and neck; SOC = standard of care.

[a] Harrington et al. 2015.

[b] Burtness et al. 2014, 2017.

[c] Tao et al. 2017.

1.3 CHECKPOINT INHIBITORS IN THE TREATMENT OF 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 susceptible to immunotherapy (Lawrence et al. 2013). SCCHN has been shown to evade the host cellular immune response through upregulation of T-cell suppressive ligands, including PD-L1, which leads to inhibition of T-cell function and tumor evasion (Ferris 2015). Nonclinical data suggests that PD-L1 expression is high in the oropharyngeal area (Lyford-Pike et al. 2013) and HPV-positive and HPV-negative SCCHN have been shown to express PD-L1 (Badoual et al. 2013; Concha-Benavente et al. 2016).

Checkpoint inhibitors have shown activity in metastatic SCCHN in the second- and third-line settings and beyond (Chow et al. 2016; Ferris et al. 2016). Both nivolumab and pembrolizumab, which target PD-1, have been approved by the U.S. Food and Drug Administration (FDA) for 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 on 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%. Response rates were 25% (4 of 16 patients; 95% CI: 7 to 52) in HPV-positive patients and 14% (4 of 29 patients; 95% CI: 4 to 32) in HPV-negative patients and all were PD-L1 positive. Two Phase III clinical trials (NCT02252042 and NCT02358031) in first-line SCCHN with pembrolizumab are ongoing.

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% CI: 0.51 to 0.96) and increased ORR (13.3% vs. 5.8%) than patients treated with single-agent investigator's choice of therapy. An updated analysis for this study (minimum follow-up 11.4 months; Gillison et al. 2017) continued to demonstrate similar results: longer OS (median 7.7 vs. 5.1 months; HR: 0.71; 97.7% CI: 0.55 to 0.90) and increased ORR (13.3% vs. 5.8%). Two Phase III clinical trials (CheckMate 714, NCT02823574 and CheckMate 651, NCT02741570) in the first-line of treatment of SCCHN with nivolumab are ongoing.

A Phase III trial (JAVELIN Head & Neck 100) evaluated avelumab plus CRT followed by avelumab maintenance against placebo plus CRT in previously untreated patients with histologically confirmed LA SCCHN. Median follow-up of progression-free survival (PFS) was 14.6 months in the avelumab group and 14.8 months in the placebo group. Median PFS was not reached (95% CI: 16.9 months to not estimable) in the avelumab

group and was not reached (23 months to not estimable) in the placebo group (stratified HR: 1.21; 95% CI: 0.93 to 1.57; p=0.92), favoring the placebo group. Median follow-up for OS was 16.7 months in the avelumab group and 16.8 months in the placebo group. Median OS was not reached in both groups (Lee et al. 2021).

Atezolizumab has also shown encouraging activity in metastatic and recurrent SCHHN in Study PCD4989g (see Section 1.4.2). Based on results of these clinical studies, blockade of the PD-1/PD-L1 pathway with atezolizumab, pembrolizumab, or nivolumab has demonstrated efficacy in patients with SCCHN.

1.4 BACKGROUND ON ATEZOLIZUMAB

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

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.4.1 Summary of Clinical Studies for Atezolizumab

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies against solid tumors and hematologic malignancies. Refer to the Atezolizumab Investigator's Brochure for study descriptions and details on these clinical studies.

Study PCD4989g is a Phase Ia, multicenter, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab in patients with locally advanced or metastatic solid tumors. Expansion cohorts have included patients with multiple tumor types, including SCCHN.

1.4.2 Efficacy of Atezolizumab in Patients with SCCHN

Study PCD4989g initially enrolled patients with metastatic SCCHN, regardless of PD-L1 status (n = 10) (Bahleda et al. 2017). Once PD-L1 was identified as a potential biomarker, patients were then selected by PD-L1 status (≥ 5% PD-L1 expression on tumor-infiltrating immune cells [ICs], i.e., IC2/3) (n = 22). Patients received atezolizumab intravenously Q3W (15 or 20 mg/kg or 1200 mg). Objective response and disease progression were determined using investigator-assessed Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

With a minimum 14-month follow-up, there were 32 efficacy-evaluable patients with SCCHN as of 31 December 2016. Of these 32 patients, 84% were male, 66% had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1, and 34% had EGOG PS of 0. The median age was 62 years (range: 32–78 years), patients were heavily pretreated (53% had ≥ 2 prior lines of therapy), and 66% were current or former tobacco users. Primary tumor sites included the oropharynx (50%), oral cavity (22%), nasopharynx (19%), larynx (6%), and hypopharynx (3%). Of the 32 patients, 41% were HPV-positive, 28% were HPV-negative, and 31% had unknown HPV status.

In all patients (IC0/1, n = 7; IC2/3, n = 25), the confirmed ORR was 22% (95% CI: 9.3%–40.0%), the median PFS was 2.6 months (range: 0.5–48.4 months), and the median OS was 6.0 months (range: 0.5–51.6 months, censored value). Clinical activity by PD–L1 subgroups (IC0/1, n = 7; IC2/3, n = 25) is shown in Table 2. Encouraging response and long-term survival were shown in recurrent and metastatic SCCHN independently of PD–L1 immunohistochemistry (IHC) or HPV status and warrant further investigation.

Table 2 Clinical Activity by PD-L1 Subgroup in SCCHN Cohort of Study PCD4989g

	IC0/1 (n=7)	IC2/3 (n=25)
ORR, n (%)	1 (14)	6 (24)
CR	0	0
PR	1 (14)	6 (24)
DCR, n (%)	3 (43)	7 (28)
mDOR, months (range)[a]	7.4	26.2 (2.8–45.8)
mPFS, months (range)	5.7 (0.5–13.5)	2.6 (0.5–48.4)
mOS, months (range)	9.0 (0.5–26.5)	5.6 (1.1–51.6+)
1-year OS rate	43%	34%
2-year OS rate	29%	18%
3-year OS rate	NE	18%

CR=complete response; DCR=disease control rate; DOR=duration of response; IC=tumor-infiltrating immune cell; mDOR=median duration of response; mOS=median overall survival; mPFS=median progression-free survival; NE=not estimable; ORR=objective response rate; OS=overall survival; +=censored value; PR=partial response; SCCHN=squamous cell carcinoma of the head and neck; SD=stable disease.

Notes: IC0=PD-L1 expression on <1%; IC1=≥1% to <5%; IC2=≥5% to <10%; IC3=≥10%. PD-L1 subgroups do not reflect the natural prevalence as not enrolled as an all-comer cohort (unselected population).

DCR refers to the percentage of patients with a CR, a PR, and SD ≥24 weeks.

[a] n=1 for IC0/1, therefore 7.4 months represent the DOR of this single patient; n=6 for IC2/3.

1.4.3 Safety of Atezolizumab Monotherapy in Patients with SCCHN

The safety of atezolizumab in SCCHN is being evaluated in Study PCD4989g (Bahleda et al. 2017). As of 31 December 2016, safety data were available for 32 patients.

Of the 32 patients, 31 patients (96.9%) reported at least one adverse event. Grade 1 or 2 events were reported in 9 patients (28.1%) and Grade 3 or 4 were reported in 20 patients (62.5%). The most commonly reported adverse events (≥10% of patients) were fatigue, decreased appetite, diarrhea, anemia, constipation, dysphagia, dyspnea, nausea, rash, headache, pyrexia, vomiting, back pain, chills, cough, abdominal pain, arthralgia, asthenia, influenza like illness, insomnia, neck pain, tumor pain, and urinary tract infection. The most commonly reported Grade 3 and Grade 4 adverse events (2 patients each) were acute kidney injury, anemia, atrial fibrillation, cellulitis, dysphagia, hydronephrosis, hyponatremia, pneumonia, and tumor lysis syndrome. Related adverse events per study investigator were reported in 21 patients (65.6%); those reported for 3 or more patients were fatigue, asthenia, influenza-like illness, pyrexia, diarrhea, nausea, and rash. Serious adverse events occurred in 16 patients (50%), with the most common adverse events (2 patients each) being atrial fibrillation, cellulitis, and sepsis.

Related serious adverse events were reported in 3 patients (9.4%); the events were hyponatremia, tumor lysis syndrome, cardiac tamponade, and colitis.

Immune-mediated adverse events were reported in 3 patients. No Grade 3 or 4 immune-mediated adverse events were reported. Three patients developed changes in liver function tests. Three patients discontinued atezolizumab due to an adverse event; colitis, sepsis and head injury in 1 patient each. At the time of data cutoff, 26 patients (81.3%) had died. Adverse events leading to death (Grade 5) were reported in 2 patients; sepsis and head injury in 1 patient each and neither was reported to be related to atezolizumab.

Based on these safety data, atezolizumab monotherapy treatment has an acceptable safety profile in the SCCHN population and is consistent with that seen in larger populations for other tumor types. No new safety findings have been observed in the SCCHN patient population in Study PCD4989g.

1.4.4 Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

For additional information, refer to the Atezolizumab Investigator's Brochure.

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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 through 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 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 (see the Atezolizumab Investigator's Brochure for detailed efficacy results). In Study PCD4989g, a Phase Ia, dose-escalation and expansion study, encouraging response and long-term survival were shown in a cohort of patients with recurrent and metastatic SCCHN independently of PD-L1 IHC or HPV status (see Section 1.4.2) and support the rationale for treatment with atezolizumab in SCCHN.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see the Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

Given the evidence of the clinical activity of atezolizumab in advanced and metastatic SCCHN, atezolizumab offers the potential for clinical benefit in patients with SCCHN in the adjuvant setting. This study will enroll patients who are classified as high risk in order to select a population that is at greatest risk of recurrence or progression and death from SCCHN who are most likely to benefit from adjuvant atezolizumab therapy. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature, it is anticipated that adjuvant treatment with atezolizumab will have a manageable safety profile and has an acceptable benefit–risk ratio in the SCCHN population.

In the setting of the coronavirus 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 *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection*. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-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 if outcome from *SARS CoV-2 infection* is altered by cancer immunotherapy.

Severe *SARS CoV-2 infection* appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). [redacted]. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from *SARS CoV-2 infection*.

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

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

Per recommendations of the NCCN, COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a

decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. *Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).*

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of atezolizumab compared with placebo as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced SCCHN. Specific objectives and corresponding endpoints for the study are outlined in Table 3.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab compared with placebo	• Investigator-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by investigator, or death from any cause, whichever occurs first
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab compared with placebo	• OS after randomization, defined as the time from randomization to death from any cause • IRF-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurs first • IRF-assessed EFS and investigator-assessed EFS at 1, 2, 3, and 4 years • OS at 2, 3 and 5 years
• To evaluate clinical benefit in atezolizumab compared with placebo in terms of impact on HRQoL and physical functioning	• Change from baseline in physical functioning over time while receiving treatment as assessed through use of the five-item Physical Functioning subscale (Questions 1–5) of the EORTC QLQ-C30 • Change from baseline in HRQoL over time while receiving treatment as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety and tolerability of atezolizumab	• Incidence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v4.0

Table 3 Objectives and Corresponding Endpoints (cont.)

Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of atezolizumab	• Serum concentrations of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the incidence and titers of ADAs against atezolizumab	• Incidence of ADA response to atezolizumab
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• [redacted]
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate and identify biomarkers in tumor tissue and blood that are associated with response to atezolizumab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to atezolizumab (i.e., mechanism of action biomarkers), are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers (e.g., PD-L1, ctDNA, TMB, *TEFF* gene expression, and others) in tumor tissue and/or blood and efficacy, disease status, resistance, or other biomarker endpoints • Relationship between biomarkers at the time of apparent recurrence (i.e., local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or progression of disease and any immunomodulatory activity of atezolizumab (i.e., tumor-immune infiltration) in patients with confirmed recurrence or progression of disease in patients assigned to atezolizumab
Exploratory PRO Objectives	**Corresponding Endpoints**
• To evaluate health status utility scores of patients treated with atezolizumab • To evaluate evolution of treatment/disease-related symptoms over time from the patients' perspective	• Utility scores based on EQ-5D-5L (including VAS) • Change over time of treatment/disease-related symptoms, as evaluated by selected items of the EORTC QLQ-C30 and QLQ-H&N35 Questionnaires during treatment, treatment discontinuation, and survival follow-up • Other PRO endpoints (e.g., time-to-confirmed symptom deterioration, proportion of patients with clinical deterioration) to document treatment and disease burden

ADA = anti-drug antibody; ctDNA = circulating tumor DNA; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; GHS = global health status; *HRQoL = health-related quality of life;* IRF = Independent Review Facility; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PRO = patient-reported outcome; QLQ-C30 = Quality of Life–Core 30 Questionnaire; QLQ-H&N35 = Quality of Life–Head and Neck, Module 35 Questionnaire; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SCCHN = squamous cell carcinoma of the head and neck; TMB = tumor mutation burden; VAS = Visual Analog Scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study WO40242 is a global Phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy after definitive local therapy in patients with locally advanced SCCHN who are at high risk for disease recurrence or progression following definitive local therapy. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of adjuvant treatment with atezolizumab compared with placebo in patients with locally advanced SCCHN who have not progressed after receiving definitive local therapy.

Male and female patients *at least* 18 years of age who have an ECOG PS 0 or 1 and histologically confirmed SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, and who have received definitive local therapy and are classified as being at high risk for recurrence or progression are eligible for study participation (see Table 4 for eligibility requirements). The definition of high risk is based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition) and includes:

- HPV-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10-packs/year smoking history and/or ≥ 10-year smokeless tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2), regardless of tobacco use history

Table 4 Primary Site, HPV Status, AJCC Stage, 8th Edition, and Tobacco Use Requirements for Eligibility

Primary Site	HPV Status	Stage	T Status	N Status	M Status	Tobacco Use History
Oral cavity, oropharynx, larynx, or hypopharynx	Negative	IVA	T4a	N0, N1, N2a, N2b, or N2c	M0	NA
			T1, T2, or T3	N2a, N2b, or N2c	M0	NA
Oral cavity, oropharynx, larynx, or hypopharynx	Negative	IVB	T1, T2, T3, or T4a	N3a or N3b	M0	NA
			T4b	N0, N1, N2a, N2b, N2c, N3a, or N3b	M0	NA
Oropharynx	Positive	III	cT1 or cT2	cN3	M0	≥10 packs/yr smoking and/or ≥10-yr smokeless tobacco
			cT3	cN3	M0	NA
			cT4	cN0, cN1, cN2, or cN3	M0	NA
			pT3 or pT4	pN2	M0	NA

AJCC=American Joint Committee on Cancer; c=clinical staging; HPV=human papillomavirus; M=distant metastasis; N=regional lymph node; NA=not applicable; p=pathological staging; T=primary tumor.

For patients whose planned definitive local therapy begins with induction chemotherapy or concurrent CRT, radiographic staging to assess eligibility should be done before definitive local therapy. For patients whose planned definitive local therapy begins with primary surgery, pathologic staging based on primary surgery should be done to assess eligibility. In addition, the primary tumor (T) and regional lymph node (N) must be synchronous. Metachronous presentation is considered recurrence in this study, which is not permitted.

Definitive local therapy is defined as any of the following combined modality approaches:

- Primary surgery followed by either postoperative RT or postoperative concurrent CRT
- Induction chemotherapy followed by primary surgery alone (e.g., laryngectomy)
- Induction chemotherapy followed by primary surgery followed by postoperative RT or postoperative concurrent CRT

- Induction chemotherapy followed by RT or concurrent CRT
- Concurrent CRT

Salvage neck dissection is permitted for neck disease after completion of RT or concurrent CRT. Salvage laryngectomy is permitted only for patients with laryngeal or hypopharyngeal cancer after completion of RT or concurrent CRT. Salvage surgery is not considered part of initial definitive local therapy for this study.

Patients with oropharyngeal or oral cavity cancer who have persistent disease at the primary site post-concurrent CRT or post-RT are not eligible, regardless of whether or not salvage resection of the primary tumor has been received.

Agents used in definitive local therapy must include an FDA-approved or European Medicines Agency (EMA)-approved platinum agent as part of an induction regimen or an FDA-approved or EMA-approved platinum agent or anti-EGFR agent as part of concurrent therapy with RT.

Surgery alone or RT alone is not considered a definitive local therapy and is an exclusion criterion. Patients who have received neoadjuvant treatment or any systemic anti-cancer therapy without definitive local therapy (either surgery and/or radiation) for locally advanced head and neck cancer are not eligible. In addition, use of any systemic therapy after permitted definitive local therapies (defined above in Section 3.1.1) (e.g., after surgery, radiation, or concurrent CRT) is not permitted.

Patients who experience disease progression or recurrence during or following definitive local therapy are not eligible. Patients must have had a complete response (CR), partial response (PR), or stable disease (SD) as assessed in comparison to scans done prior to definitive local therapy. Both response in the head and neck region (performed via magnetic resonance imaging [MRI] with contrast or computed tomography [CT] with contrast) and absence of metastasis outside of the head and neck region (performed via CT with contrast of the chest and abdomen) must be documented on scans performed ≥ 8 weeks (56 days) after completing definitive local therapy, and within 28 days prior to initiation of study drug (patients who receive salvage surgery must have screening scans after salvage surgery).

Patients who have an equivocal response after definitive local therapy at their post-definitive local therapy scans (done at screening) should receive further evaluation (e.g., positron emission tomography [PET] scans) per local standard as well as a biopsy if indicated. Investigators may use the PET scan and/or biopsy results, if performed, to inform their assessment of the screening CT and/or MRI scans. If the assessment is still equivocal, that patient is not eligible.

Patients must initiate study treatment within 28 days of the screening scans and within 16 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was not performed) or within 20 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was performed); also refer to Table 5. The date of completion of definitive local therapy is exclusive of salvage surgery.

Table 5 Timing for Post-Definitive Local Therapy Screening Scans and Initiation of Study Treatment

Salvage Surgery	Time from Completing Definitive Local Therapy to Screening Scan [a]	Time from Completing Definitive Local Therapy to Initiation of Study Treatment
No	8–16 weeks	≤16 weeks
Yes	8–20 weeks	≤20 weeks

[a] Screening scans must be done within 4 weeks (28 days) of initiation of study treatment. Screening scans for patients who receive salvage surgery must be done after salvage surgery.

Approximately 406 patients globally will be randomized. All patients will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): atezolizumab 1200 mg Q3W
- Arm B (control arm): placebo Q3W

Randomization will be stratified by the following factors:

- Response to definitive local therapy (CR vs. PR or SD)

  In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

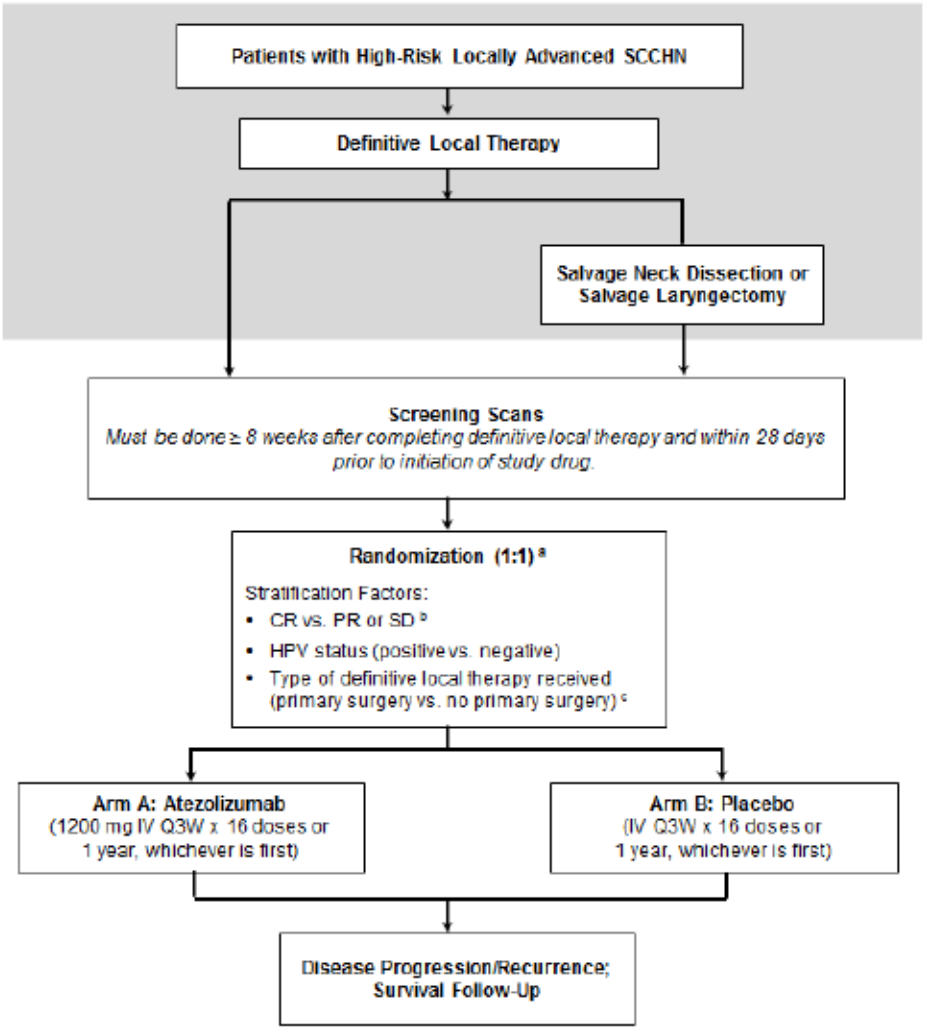
- HPV status (positive vs. negative)

  Patients with HPV-positive oropharyngeal carcinoma will be capped at 20%.

- Type of definitive local therapy received (primary surgery vs. no primary surgery)
  - Primary surgery: Patients who received a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, regardless of whether a salvage surgery was received.
  - No primary surgery: Patients who did not receive a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy but may or may not have had a salvage surgery.

For patients to be eligible, a representative pretreatment tumor specimen for exploratory biomarker research must be available and confirmed before the randomization. The tissue sample must be submitted within 4 weeks after randomization. Figure 1 presents an overview of the study design.

Figure 1 Study Schema



C1D1 = Cycle 1, Day 1; CR = complete response; CRT = chemoradiotherapy; HPV = human papillomavirus; PD = progressive disease; PR = partial response; Q3W = every 3 weeks; RT = radiotherapy; SCCHN = squamous cell carcinoma of the head and neck; SD = stable disease.
Note: Shaded box indicates off-study treatments.

[a] Patients must initiate study treatment (C1D1) within 28 days of the screening scans (post-definitive local therapy scans), and within 16 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was not performed) or within 20 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was performed). The date of completion of definitive local therapy is exclusive of salvage surgery.

[b] In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

[c] Primary surgery: primary surgery followed by either postoperative RT or postoperative concurrent CRT, induction chemotherapy followed by primary surgery alone, or induction chemotherapy followed by primary surgery followed by RT or concurrent CRT. No primary surgery: induction chemotherapy followed by RT or concurrent CRT, concurrent CRT alone, or any of the aforementioned modalities followed by salvage neck dissection or salvage laryngectomy (salvage laryngectomy is only for patients with laryngeal or hypopharyngeal cancer).

Patients in both treatment arms will receive 16 cycles or up to 1 year (whichever occurs first) of treatment with either atezolizumab (fixed dose of 1200 mg) or placebo. Treatment will be administered by IV infusion on Day 1 of each 21-day cycle. Treatment will be discontinued in the event of disease recurrence (i.e., local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor.

The primary endpoint of this study will be investigator-assessed event-free survival (EFS). Patients will undergo scheduled tumor assessments (see Section 4.5.5 and Appendix 1 for details) by means of imaging at baseline and every 9 weeks following Day 1, Cycle 1 (every three cycles) for the first 2 years. Tumor assessments will occur every 12 weeks during Year 3, every 16 weeks during Years 4 and 5, and annually thereafter at the investigator's discretion as clinically indicated. Tumor assessments will continue per schedule regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started) until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per RECIST v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are randomized with evidence of residual disease at baseline (as assessed by screening scans, detailed in Figure 1 and Table 5) will be assessed for disease progression according to RECIST v1.1. For patients who are randomized with no evidence of disease at baseline (as assessed by screening scans), disease recurrence will be determined and confirmed based on unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis. All patients will undergo a physical examination Q3W, and if recurrent or progressive disease is suspected based on clinical grounds, tumor assessments must be performed expeditiously, even if not mandated in the schedule of activities. In cases of equivocal radiographic evidence of recurrence or progression, recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated.

To capture disease and treatment burden, patients will complete selected items from the validated and reliable European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30; Aaronson et al. 1993; Fitzsimmons et al. 1999) and the Quality of Life–Head and Neck, Module 35 Questionnaire (QLQ-H&N35; Bottomley et al. 2014). In addition, the EuroQol Dimension, 5-Level Questionnaire (EQ-5D-5L) including the health status Visual Analog Scale (VAS) will be collected for health economic modeling purposes.

Safety assessments will include the incidence, nature, and severity of adverse events, changes in vital signs, and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

[redacted]

After study treatment discontinuation, survival status, subsequent anti-cancer therapies (including targeted therapies and immunotherapies), and patient-reported outcomes (PROs) will be collected for all patients until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

The schedules of activities are provided in Appendix 1 and Appendix 2.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data and interim futility and efficacy analyses for investigator-assessed EFS according to policies and procedures detailed in an iDMC Charter.

3.2 END OF STUDY AND *DURATION OF PARTICIPATION*

The end of this study will occur when both of the following criteria have been met:

- The last patient, last visit has occurred.
- Approximately 191 deaths have occurred in the intent-to-treat (ITT) population.

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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 111 months.

The total duration of study participation for each individual is expected to range from 1 day to approximately 111 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab monotherapy (Tecentriq® U.S. Package Insert; Tecentriq Summary of Product Characteristics). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

The duration of time required to eradicate micro-metastatic disease or an effective anti-tumor response in the adjuvant setting through PD-L1 inhibition is currently unclear.

However, given the high risk of recurrence in the SCCHN population under study and the existing safety profile of atezolizumab, a 1-year period of adjuvant treatment has been selected because this is believed to balance the risks and tolerability of therapy with the expected benefit. In addition, other adjuvant SCCHN studies commonly utilize 1 year of adjuvant therapy (see Table 1).

3.3.2 Rationale for Patient Population

There is currently no approved, effective adjuvant treatment for SCCHN, and locally advanced (Stage III–IVB) SCCHN is associated with a high risk for both local recurrence and distant metastases. Locally advanced disease is associated with a poor outcome (median OS of approximately 20 months; Adelstein et al. 2003). Patients with HPV-negative Stage IVA and IVB disease have a 5-year survival rate of < 25% (Denis et al. 2004), and patients with HPV-positive oropharyngeal carcinoma with Stage III disease have a 5-year survival rate of 50% (Vokes et al. 2015; O'Sullivan et al. 2016).

Locally advanced SCCHN is associated with a poor outcome and patients treated with definitive local therapy have a 65% risk of recurrence in 5 years (Adelstein et al. 2003). Treatment of locally advanced SCCHN includes definitive local therapy that consists of combined modality approaches to optimize the chances for long-term disease control. After definitive local therapy is received, the NCCN guidelines (2017) or ESMO guidelines (Grégoire et al. 2010) do not recommend any additional therapy, and the current standard of care is observation to monitor patients for local recurrence and/or distant metastases.

This study will enroll patients, irrespective of PD-L1 expression status, who have received definitive local therapy for locally advanced SCCHN and who are considered to be at high risk for disease recurrence or progression based on staging by the AJCC Cancer Staging Manual, 8th edition and will include:

- HPV-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10-packs/year smoking history and/or ≥ 10-year smokeless tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2), regardless of tobacco use history

The study assumptions are determined based on recently published data. In the Phase III trial LUX-Head & Neck 2 (NCT01345669), 617 patients with Stage III, IVA or IVB intermediate- to high-risk SCCHN who had complete response after CRT, with or without resection of residual disease, were randomized to receive either adjuvant afatinib or placebo. At study termination, median DFS was 43.4 months (afatinib) and not

estimable (control), while the 2-year disease-free probability was 67.2% and 73.5%, respectively. OS were immature with not estimable median OS for both arms (Burtness et al. 2019). In the Phase III trial (JAVELIN Head & Neck 100, NCT02952586) of avelumab plus standard-of-care CRT versus CRT alone in 697 patients with Stage III and Stage IV T1–T4 tumors and N0–N3 lymph nodes, median PFS and median OS were not reached in both arms at study termination (median follow-up time: 14.8 months) (Lee et al. 2021). The long-term report of the Phase III trial (RTOG0129, NCT00047008) of cisplatin plus accelerated fractionation with a concomitant boost versus stand fractionation in 721 patients with Stage III and Stage IV (T1 and T2N1 tumors excluded) suggests median PFS could be approximately 4.5 years with a median follow-up time of 7.9 years. The 5-year OS rate was 56.6%–60.0% (Nguyen-Tan et al. 2014). On the basis of these studies, the median EFS and median OS for the control arm in this study are assumed to be 40 months and 70 months, respectively.

Rationale for PD-L1 Unselected Population

This study will enroll patients with locally advanced SCCHN whose tumor tissue is available for PD-L1 expression testing by IHC at a central laboratory, but randomization and stratification are irrespective of PD-L1 expression status.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several tumor types (Topalian et al. 2012; Herbst et al. 2014, 2016; Borghaei et al. 2015; Fehrenbacher et al. 2016; Rosenberg et al. 2016). However, efficacy of atezolizumab is not restricted to tumors that overexpress PD-L1 (Rittmeyer et al. 2017) and preliminary data from Study PCD4989g (see Section 1.4.2) suggest efficacy of atezolizumab in SCCHN irrespective of PD-L1 status. The relationship between PD-L1 expression and efficacy in SCCHN is continuing to evolve. Inconsistent correlation was observed with PD-L1 expression and efficacy of nivolumab or pembrolizumab in metastatic or recurrent SCCHN (Ferris et al. 2016; Bauml et al. 2017). Since benefit is not anticipated to be limited to patients with high PD-L1 expression, this study will enroll patients with locally advanced SCCHN, regardless of PD-L1 expression. The inclusion of patients with all levels of PD-L1 expression by IHC in this study will enable evaluation of EFS in the overall population with atezolizumab treatment relative to placebo treatment irrespective of PD-L1 status. Tumor tissue and blood will be collected as a requirement for exploratory analysis to study the relationship between biomarkers (including PD-L1, circulating tumor DNA (ctDNA), tumor mutational burden (TMB), *TEFF* gene signature) and efficacy, disease status, resistance, or other biomarker endpoints.

3.3.3 Rationale for Placebo-Control Arm and Blinded Design

Observation is the standard of care after definitive local therapy for patients with locally advanced SCCHN. According to NCCN Guidelines in oncology for head and neck cancers (Version 2; 2017) and ESMO guidelines (Grégoire et al. 2010), there are no standard adjuvant therapies, and clinical study participation should be encouraged. Use of adjuvant chemotherapy for patients with SCCHN is not listed in current EU and U.S. guidelines. For patients who have been treated with definitive local therapy for locally advanced SCCHN and have achieved a response, there is currently no standard active treatment for these patients in the adjuvant setting.

The Sponsor has chosen a double-blinded study design with placebo as control rather than an open-label study design with observation as the control primarily given the advantages of double-blinded control studies in reducing potential bias in the assessment of disease recurrence or progression, PROs, and safety. Additional advantages include reduced chances of dropout (attrition) and improved study retention for follow-up in the control arm, as well as the potential to minimize the risk of off-label use of currently approved therapies in metastatic setting. Maintaining optimal study follow-up may be a considerable concern with an observation only arm, and this may also introduce unforeseen potential biases in investigator assessments. The choice of a placebo arm will allow maintenance of effective scientific integrity and rigor.

To minimize bias in the timing of key assessments of safety and efficacy, patients in the placebo arm will receive placebo and will undergo assessments conducted on the same schedule as patients in the atezolizumab arm.

3.3.4 Rationale for Stratification Factors

In order to balance the disease-related risk factors between the two treatment arms, randomization will be stratified. The proposed stratification factors are as follows:

- Response to definitive local therapy (CR vs. PR or SD)

  In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

- HPV status (positive vs. negative)

  Patients with HPV-positive oropharyngeal carcinoma will be capped at 20%.

- Type of definitive local therapy received (primary surgery vs. no primary surgery)
  - Primary surgery: patients who received a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, regardless of whether a salvage surgery was received
  - No primary surgery: patients who did not receive a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, but may or may not have had a salvage surgery

These factors are critically important prognostically for patients with SCCHN and therefore are proposed to be included in the study for the following reasons:

- The response to definitive local therapy (CR vs. PR or SD) has been added as a stratification factor to control for any differences associated with prognostic outcome for patients that have SD after receiving definitive local therapy in comparison with patients who have experienced a PR or CR after definitive local therapy.
- HPV status is a prognostic indicator and patients with HPV-positive oropharyngeal carcinoma have a relatively better prognosis. Therefore, HPV status has been included as a stratification to control for any differences in outcome (Vokes et al. 2015; O'Sullivan et al. 2016). Patients with HPV-positive oropharyngeal carcinoma will be limited to 20% of the randomized population. A 20% cap is being put in place since the prevalence of HPV-positive oropharyngeal carcinoma is higher in the Western world in comparison with the rest of the world where tobacco-associated SCCHN is more common. Therefore, limiting patients with HPV-positive oropharyngeal carcinoma will provide a population more representative of the distribution of SCCHN globally.
- Patients who have a response to surgery followed by RT or CRT tend to have a better prognosis than patients who undergo induction therapy followed by CRT or CRT alone. Therefore, patients are stratified according to whether they receive primary surgery as part of definitive local therapy.

3.3.5 Rationale for Event-Free Survival as the Primary Endpoint

In this study, the primary endpoint is investigator-assessed EFS. This study will evaluate whether treatment with atezolizumab will prolong EFS compared with treatment with placebo.

Disease-free survival and PFS are common endpoints in adjuvant trials since they measure time to a specific event: disease recurrence in patients without disease at study start or time to progression in patients with disease burden at study start, respectively. When a study enrolls patients with or without evidence of disease at the enrollment, EFS can be used to assess the disease recurrence or progression. This endpoint has been used in SCCHN adjuvant studies (e.g., NCT03040999/KEYNOTE-412) and has been chosen as a primary endpoint for this study. Patients either will or will not have evidence of disease at the time of randomization. EFS is defined as the time from randomization to:

- Time to first disease progression event per RECIST v1.1 in patients with evidence of residual disease at the time of randomization.
- Time to first disease recurrence event per radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis in patients with no evidence of disease at the time of randomization.
- Clinical evidence of recurrent disease must be confirmed by radiographic scans.
- Time to death (if death occurs without disease recurrence or progression).

Based on available data for adjuvant therapies in this patient population, OS is likely to be prolonged and hence OS may not be an appropriate primary endpoint (FDA 2018; EMA 2019). EFS as an endpoint can reflect tumor recurrence or growth with good predictive value for survival benefit and can be assessed before the determination of a survival benefit; additionally, its determination is less confounded by subsequent non–protocol-specified anti-cancer therapies than OS. OS will be designated as a key secondary endpoint. This approach has also been adopted in other SCCHN adjuvant studies (Machiels et al. 2020; Lee et al. 2021). The Statistical Analysis Plan (SAP) (see Section 6) has been aligned to this approach.

The Sponsor will use EFS as the primary endpoint in this study. This endpoint is very well established and robust and is shown to be valuable in evaluating the efficacy of cancer immunotherapy. Therefore, the Sponsor believes that having EFS as the primary endpoint is the preferred approach to appropriately assess the efficacy of atezolizumab for the treatment of patients with locally advanced SCCHN in the adjuvant setting.

3.3.6 Rationale for Biomarker Assessments

The primary objective of this study is to evaluate efficacy of atezolizumab in the ITT population. However, exploratory biomarker analyses are also planned. The relationship between PD-L1 expression and efficacy in SCCHN is continuing to evolve. Inconsistent correlation was observed (ITT) with PD-L1 expression and efficacy of nivolumab or pembrolizumab in metastatic or recurrent SCCHN (Ferris et al. 2016; Bauml et al. 2017).

In other tumor types, published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016), with survival benefit observed across all levels of PD-L1 expression (Rittmeyer et al. 2017).

In addition, higher expression of genes related to PD-L1 and T-effector biology in tumor tissue is associated with improved efficacy of atezolizumab compared with docetaxel in NSCLC (Fehrenbacher et al. 2016). Similar observations have been reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015). Furthermore, expression of PD-L1 on ICs was reported to be associated with expression of a T-effector gene signature, therefore representing a preexisting immunity (Fehrenbacher et al. 2016).

In the current study, archival or baseline freshly collected pretreatment tumor specimens will be collected from patients and may be tested for PD-L1, TMB, and/or T-effector gene expression by a central laboratory. In addition, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Blood samples will be collected at baseline and during the study to evaluate surrogate biomarkers. Biomarkers such as tumor mutational burden and analysis of ctDNA may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples (and their derivatives) may be analyzed through use of next-generation sequencing (NGS), including but not limited to, whole exome sequencing (WES), to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

3.3.7 Rationale for Patient-Reported Outcome Assessments

Patients with head and neck cancers report changes in speech, swallowing or breathing as a result of the tumor expansion, surgical resection, or radiochemotherapy. Changes in basic functions such as eating or speaking associated with physical appearances sequelae with facial disfigurement from therapy contribute to the report of decreased functioning in daily activities and decline of health-related quality of life (Hecker et al. 2002; Campbell et al. 2000). Thus, NCCN guidelines (2017) recommend not only following patients post-resection for possible recurrence, but also for assessment of their health behaviors, nutrition, dental health and speech, and swallowing function.

Selected scales from the well-established patient-completed questionnaires (EORTC QLQ-C30 and QLQ-H&N35) will be administered across both treatment arms throughout the study, including at treatment discontinuation and long-term survival follow-up (see Appendix 4 and Appendix 5). Collection of PROs will not only be used to assess the severity of commonly reported symptoms of head and neck cancer and its treatment, but also the impact of these symptoms on patients' functioning and global health status (GHS) and QoL to further inform the benefit–risk assessment of atezolizumab from the perspective of the patients.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 406 patients with high-risk locally advanced SCCHN.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

- Age ≥ 18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed SCCHN (HPV-positive Stage III oropharyngeal carcinoma or HPV-negative Stage IVA or IVB involving the oral cavity, oropharynx, larynx, or hypopharynx based on AJCC 8th Edition Cancer Staging Manual)

  The primary tumor and cervical nodes must be present synchronously and eligible patients must meet one of the following criteria (see Table 4):

  – HPV-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
  – HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
  – HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10-packs/year smoking history and/or ≥ 10-year smokeless tobacco use history
  – HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2), regardless of tobacco use history
- HPV status, as determined locally by p16 IHC, in situ hybridization, or by polymerase chain reaction–based assay
- Completed definitive local therapy (as defined below):
  – Primary surgery followed by either postoperative RT or postoperative concurrent CRT
  – Induction chemotherapy followed by primary surgery alone (e.g., laryngectomy)
  – Induction chemotherapy followed by primary surgery followed by postoperative RT or postoperative concurrent CRT
  – Induction chemotherapy followed by RT or concurrent CRT
  – Concurrent CRT

    Notes: Salvage neck dissection is permitted for neck disease after completion of RT or concurrent CRT. Salvage laryngectomy is permitted only for patients with laryngeal or hypopharyngeal cancer after completion of RT or concurrent CRT.

    Agents used in definitive local therapy must include an FDA- or EMA-approved platinum agent as part of an induction regimen or an FDA- or EMA-approved platinum agent or anti-EGFR agent as part of concurrent therapy with RT.
- Absence of metastatic disease as confirmed by negative CT with contrast of chest and abdomen within 28 days prior to initiation of study drug (for patients with a contraindication to CT with contrast, see Section 4.5.5)

Note: Patients with a contraindication to both CT with contrast and MRI may be eligible; see Section 4.5.5 for scanning requirements.

- Recovered from acute toxicities associated with definitive treatment to Grade 1 or lower, except fatigue, xerostomia, dysgeusia, alopecia, and toxicities related to prior treatment requiring management with a feeding tube

  Patients with feeding tubes are eligible.

- Availability of a representative pretreatment tumor specimen for exploratory biomarker research (see Section 4.5.6 for information on tumor specimens) must be confirmed

  The tissue sample must be submitted within 4 weeks after randomization.

- ECOG PS of 0 or 1
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.3 \times 10^9$/L (300/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Creatinine CL ≥ 20 mL/min (calculated per institutional guidelines or according to the Cockcroft-Gault or Modification of Diet in Renal Disease formula)
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

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

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

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

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

  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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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.

- Confirmed response of CR, PR, or SD to definitive local therapy (as compared to scans done prior to definitive local therapy) documented by CT with contrast or MRI with contrast of head and neck region done ≥ 8 weeks after completion of definitive local therapy and within 28 days prior to initiation of study drug

  If salvage neck dissection or salvage laryngectomy is not performed, patients must initiate study treatment (i.e., Day 1 of Cycle 1) within 16 weeks after completion of definitive local therapy.

  If salvage neck dissection or salvage laryngectomy is performed, patients must initiate study treatment within 20 weeks after completion of definitive local therapy.

  For patients who may require a salvage surgery for residual disease, the evaluation for salvage surgery must be completed and decision on whether a salvage surgery is needed must be made prior to randomization.

  Note: Patients with a contraindication to both CT with contrast and MRI may be eligible (see Section 4.5.5 for scanning requirements).

4.1.2 Exclusion Criteria

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

- Patients who have received surgery alone or RT alone as definitive local therapy

- HPV-negative patients who have a TX tumor or NX nodal stage
- HPV-positive oropharyngeal carcinoma patients who have a clinical T0 tumor or NX nodal stage, or pathological NX, N0, or N1 nodal stage
- Patients with oropharyngeal or oral cavity cancer who have persistent disease at the primary site post-concurrent CRT or post-RT, regardless of whether or not salvage resection of the primary tumor has been received
- Squamous cell carcinoma of the nasopharynx or paranasal sinuses or non-squamous histology
- Evidence of disease progression or metastatic disease during or following definitive local therapy documented in the post-definitive local therapy screening scans
- Uncontrolled or symptomatic hypercalcemia
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7 for a more comprehensive list of autoimmune diseases and immune deficiencies), 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 CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

- Major surgical procedure, other than for diagnosis or salvage neck dissection or salvage laryngectomy, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy, including prior SCCHN primary tumors (other than current SCCHN) within 5 years prior to screening

  Patients who have malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years) are eligible provided they meet all of the following criteria:

  – Malignancy treated with expected curative intent, 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

  – No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
- 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
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) may be eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Prior neoadjuvant (i.e., induction) treatment or any systemic anti-cancer therapy without definitive local therapy (either surgery and/or radiation) for locally advanced head and neck cancer
- Treatment with investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–α [anti–TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) *are* eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

  Patients who are receiving low-dose (equivalent to ≤ 10mg prednisone a day) corticosteroids for radiation induced mucositis, or mucosal edema are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the last dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Patients who have received a non–FDA- or non–EMA-approved anti-EGFR agent or any other non–FDA- or non–EMA-approved agent as part of definitive local therapy unless the unapproved agent was given in addition to an approved platinum agent as part of an induction regimen or in addition to an approved platinum or anti-EGFR agent as part of concurrent therapy with RT
- Any systemic therapy after permitted definitive local therapies (defined in Section 3.1.1) (e.g., after surgery, radiation, or concurrent CRT)

  For patients who receive concurrent CRT as definitive local therapy, any systemic therapy administered >7 days after the last date of radiation is not permitted.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a randomized, double-blind, placebo-controlled study. After 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 from the interactive voice or web-based response system (IxRS).

Patients will be randomized in a 1:1 ratio to one of two treatment arms: atezolizumab or placebo. Randomization will be stratified by the following factors:

- Response to definitive local therapy (CR vs. PR or SD)

  In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

- HPV status (positive vs. negative)

  Patients with HPV-positive oropharyngeal carcinoma will be capped at 20%.

- Type of definitive local therapy received (primary surgery vs. no primary surgery)
  - Primary surgery: Patients who received a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, regardless of whether a salvage surgery was received
  - No primary surgery: Patients who did not receive a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, but may or may not have had a salvage surgery

A permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm within levels of the stratification factors. Patients with HPV-positive oropharyngeal carcinoma will be limited to 20% of study population.

Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 4 days after randomization.

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, the external independent statistical coordinating center (responsible for verifying patient randomization and study treatment kit assignments), and iDMC members.

While PK and ADA samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples may be analyzed for all patients. Postbaseline

ADA samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

4.2.1 Unblinding at the Patient Level

All occurrences of unblinding, including their date, time, and rationale, should be documented in the study file. Unblinding of treatment assignment may only occur under the following circumstances.

4.2.1.1 Emergency Unblinding

Per health authority reporting requirements, treatment assignment will be unblinded for serious, unexpected study drug–related toxicity (e.g., as part of the Investigational New Drug [IND] safety reporting process). In these instances, investigators will not be notified of individual patient's treatment assignments as a matter of course.

Emergency unblinding by the investigator should be performed only in cases when knowledge of treatment assignment will affect the management of a patient who experiences a treatment emergent adverse event. Investigators are encouraged to consult with the Medical Monitor prior to performing emergency unblinding. If unblinding is necessary for patient safety management, the investigator is authorized to break the treatment code within the IxRS solely for the patient experiencing the treatment-emergent adverse event. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

Unblinding should not result in the withdrawal of the patients from the study. Every effort should be made to retain unblinded patients and continue data collection as per protocol.

4.2.1.2 Unblinding upon Disease Recurrence or Progression

Prior to disease recurrence or progression, patients' treatment allocation must remain blinded.

Upon disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or progression (per unequivocal radiographic evidence as assessed by RECIST v1.1) and discontinuation of study treatment, the study drug assignment may be unblinded (for patients with confirmed disease recurrence or progression only) provided that the following conditions are met:

- There is a plan to treat the patient with next line of treatment that includes another checkpoint inhibitor, which is approved as the next line of treatment, or enrolling her or him in a subsequent clinical trial; and
- There is documented evidence that the patient meets the eligibility criteria for the next line of treatment with a checkpoint inhibitor, which is approved as the next line of treatment, or clinical trial; and

- The knowledge of treatment allocation (atezolizumab/placebo) in the current study is required to confirm eligibility for the next line of treatment with a checkpoint inhibitor, which is approved as the next line of treatment, or clinical trial; and
- The investigator obtains Sponsor approval for the potential unblinding.

The study center will be required to send all requests for unblinding, including documentation of radiographic disease recurrence or progression, to the Sponsor for approval. Approval of the request and unblinding of study drug assignment under this scenario will occur only during business hours.

Crossover to atezolizumab for patients allocated to placebo is not allowed upon unblinding. Unblinding should not result in the withdrawal of the patients from the study. Every effort should be made to retain unblinded patients and continue data collection as per protocol.

4.2.2 Unblinding at the Study Level

Treatment assignment will be unblinded to the Sponsor at the time of the interim analysis of the primary endpoint investigator-assessed EFS if the prespecified efficacy boundary for EFS is crossed or at the time of the final analysis of the primary endpoint of investigator-assessed EFS.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab and placebo. *Appendix 10 identifies all investigational medicinal products for this study.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

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

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

4.3.1.2 Placebo

The placebo will be identical in appearance to atezolizumab and will comprise the same excipients but without atezolizumab Drug Product. It should be handled, stored, and used in the same manner as atezolizumab.

Placebo will be supplied by the Sponsor.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2 and in Appendix 9.

4.3.2.1 Atezolizumab and Placebo

Atezolizumab (fixed dose of 1200 mg) or placebo will be administered by IV infusion on Day 1 of each 21-day cycle for 16 cycles (or up until 1 year, whichever occurs first), or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor, whichever occurs first.

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 8. Atezolizumab infusions will be administered per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, 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. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 9.

No dose modification for atezolizumab is allowed.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and placebo) will be provided by the Sponsor where required by local health authority regulations. 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.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (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 the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide Roche IMP (atezolizumab) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated Vaccinations *(such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab 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 (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, RT, surgery, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent and during study treatment, until disease recurrence or progression is documented, and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days or 5 half-lives, whichever is longer, prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 28 days prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 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

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. 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 dose; dosing will occur only if the 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). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, tobacco use (smoking and smokeless) history, and use of alcohol, and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history, including ongoing use of tobacco (smoking and smokeless), must be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at every cycle and additionally 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.

At the time of each follow up physical examination, an interval medical history, including ongoing use of tobacco (smoking and smokeless), must be obtained and any changes in medications and allergies should be recorded.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure in the seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

Vital signs should be measured within 60 minutes prior to each atezolizumab/placebo infusion and, if clinically indicated, during or after the infusion (see Table 6). In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor Assessments

All patients will undergo scheduled tumor assessments at baseline and every 9 weeks counted, starting on Day 1 of Cycle 1 for 2 years. Tumor assessments will occur every 12 weeks during Year 3, every 16 weeks during Years 4 and 5, and annually thereafter

at the investigator's discretion if clinically indicated. Tumor assessments will continue per schedule, regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started), until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per RECIST v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. In addition, if recurrence or progression of disease is suspected based on clinical evidence, protocol required imaging must be performed expeditiously, even if not mandated in the schedule of activities. Protocol-required imaging (e.g., CT and/or MRI) is to continue according to schedule in patients who discontinue treatment for clinical decline or any other reason in the absence of radiographic disease recurrence or progression.

All measurable and non-measurable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

The head and neck region, chest, and abdomen must all be evaluated during screening. Radiographic assessments of the head and neck region utilizing either CT scans (with oral or IV contrast) or MRI with contrast are required. Radiographic assessments must also include CT scans (with oral or IV contrast) of the chest and abdomen. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy), a non-contrast CT scan of the chest may be performed, and MRI scans (with contrast) of the abdomen and head and neck region should be performed.

If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from Medical Monitor.

Patients who have an equivocal response after definitive local therapy at their post-definitive local therapy scans (done at study screening) should receive further evaluation (e.g., PET scans) per local standard as well as a biopsy if indicated. Investigators may use the PET scan and/or biopsy results, if performed, to inform their assessment of the screening CT and/or MRI scans. If the assessment is still equivocal, the patient is not eligible.

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

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

tumor assessments. All measurable and non-measurable lesions should be re-assessed at each subsequent tumor evaluation. Imaging of the head and neck region and chest must be performed at every scheduled tumor assessment. Imaging of the abdomen and bone must be performed as clinically indicated, and imaging of the abdomen must be done upon documentation of recurrent or progressive disease in the head and neck region and/or chest.

Progression of patients with evidence of residual disease at baseline (as assessed by screening scans) will be assessed by the investigator using RECIST v1.1 (Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Disease recurrence in patients with no evidence of disease at baseline (as assessed by screening scans, detailed in Figure 1 and Table 5) will be determined by the investigator based on unequivocal radiographic evidence of recurrence (local recurrence, new second primary SCCHN lesion, or development of distant metastasis).

In cases of equivocal evidence of disease recurrence or progression, disease recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated. Tumor biopsies may be performed if clinically required to confirm disease recurrence or progression.

All scans must be submitted to the IRF for independent review.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum): sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the site), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH
- Coagulation: INR, aPTT
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

- HPV status of tumor tissue determined by any of the following methods: p16 IHC, in situ hybridization, or polymerase chain reaction based assay

  If HPV status by p16 IHC, in situ hybridization, or polymerase chain reaction based assay is unknown, archival tumor tissue or freshly collected tumor tissue must be tested at screening.

  Analysis of HPV will be performed using an assay that may be considered investigational per local regulations.

- Pregnancy test

  All women of childbearing potential, including women who have had a tubal ligation, will have a serum pregnancy test at screening. Either urine or serum pregnancy tests must be performed at every cycle during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of validated assays
- Blood, plasma, and serum samples for exploratory research on biomarkers

  Blood samples may be processed to obtain plasma, serum, peripheral blood mononuclear cells (PBMCs) and other derivatives (e.g., RNA, DNA, etc.).

- Archival or freshly collected pretreatment tumor tissue sample obtained at baseline for exploratory research on biomarkers

  The specimen must be accompanied by the associated pathology report. The pretreatment tumor tissue (archival or freshly obtained) sample should be submitted within 4 weeks after randomization.

  Although any available tumor tissue sample can be submitted, sites are strongly encouraged to submit a representative formalin-fixed, paraffin-embedded tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections.

  If resection specimen is not available, patients can submit tumor specimens from a core needle biopsy collected prior to study randomization.

  If patient is not a surgical candidate or tissue is not available from resection or biopsy, any representative tissue sample can be submitted.

  Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. If these sample types are not available, any type of specimen (e.g., fine-needle aspiration) is acceptable. Tumor tissue should preferably be of good quality based on total and viable tumor content.

Exploratory biomarker research in tumor tissue and blood may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, markers associated with T-cell activation, or density, localization, and activation status of immune cells and their subsets, and may involve extraction of DNA, circulating tumor DNA or RNA, analysis of somatic mutations, and use of NGS (including, but not limited to, WES).

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), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and fresh tumor tissue samples and their derivatives collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks 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 exploratory 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.

4.5.7 Electrocardiograms

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

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

4.5.8 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of select scales from the EORTC QLQ-C30 and QLQ-H&N35, and the full EQ-5D-5L. The questionnaires will be translated as appropriate into the local language.

Only selected scales with a total of 27 items from these two measures instead of the 65 items will be administered to minimize patient response burden (response fatigue), to avoid concept redundancy (e.g., two scales assessing pain severity), to improve content validity (e.g., item referring to different food textures that might not be applicable across the population), and to improve patients' compliance in rating the burden associated with their disease and treatment.

Paper PRO questionnaires scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to other study assessments and before administration of study treatment to avoid as much as possible, any assessment bias. Patients will complete paper versions of the questionnaires, which will be provided by site staff. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to

complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Appropriate translated versions of the local language of the PRO measures will be available at the site.

4.5.8.1 EORTC QLQ-C30, Modified and QLQ-H&N35, Modified

The EORTC QLQ-C30 is a widely used PRO instrument that is modular in its design, with individual symptom scales and items as well as GHS/QoL and five functional scales scored separately. The QLQ-H&N35 follows the same structure as the EORTC QLQ-C30 while capturing symptoms and functional impacts that are specific to patients with cancer in the head or neck region. The EORTC QLQ-C30 and the QLQ-H&N35 are validated and reliable self-reported measures (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999; Bottomley et al. 2014).

Only selected scales from the EORTC QLQ-C30 (including Global GHS/QoL, Physical Function, Social Function, Dyspnea, Appetite Loss, and Fatigue) and from the QLQ-H&N35 (including Pain, Pain Killers, Dry Mouth, Sticky Saliva, Choking, Senses Problems, and Speech Problems) that capture the most relevant concepts for this population will be collected from patients at study drug administration visits and at treatment discontinuation.

To further minimize burden to patients and only after treatment discontinuation, only the GHS/QoL scale (Questions 29 and 30) and the Physical Functioning scale (Questions 1–5) of the EORTC-QLQ-C30 will be administered to patients as described in Section 4.6.1.1.

The EORTC QLQ-C30 and QLQ-H&N35 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Scale scores will be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

4.5.8.2 EQ-5D-5L

The EQ-5D-5L is a validated health status questionnaire that is used to calculate health states for use in health economic analyses (EuroQoL Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components of the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allow for the creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be completed in its entirety (including VAS) at study drug administration visits, at treatment discontinuation visit, and after treatment discontinuation as described in Section 4.6.1. The EQ-5D-5L is used in this study to inform pharmacoeconomic evaluations and, as such, will not be included in the Clinical Study Report.

4.5.9 Optional Tumor Biopsies

Consenting patients will undergo the following optional tumor biopsies (if deemed clinically feasible by the investigator) for exploratory research on biomarkers: optional tumor biopsy at the time of radiographic disease recurrence or progression, and/or any time during treatment or survival follow-up (at investigator's discretion). Biopsies at the time of disease progression or recurrence should be performed within 40 days after progression, recurrence or prior to the next anti-cancer therapy, whichever is sooner. Biopsies collected at the investigator's discretion are preferred at the time of clinical events.

Samples collected via 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.

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

Samples may be used for exploratory biomarker research as described in Section 4.5.6. Refer to Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, and confidentiality standards for data.

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

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, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression

- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 cancer immunotherapy or malignant diseases:

- Blood sample for the RBR at Cycle 1, Day 1, or as soon as possible after randomization, during the conduct of the clinical study
- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, PBMCs, proteins, peptides, etc.), including leftover tissue samples from medically indicated procedures (e.g., salvage surgery, debulking surgery, pleural fluid aspirate) performed at the investigator's discretion during the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), WES, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' 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. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

Patient medical information associated with RBR specimens 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 specimens, 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 specimens 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 consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR 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 specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study WO40242 does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from Study WO40242.

4.5.10.7 Monitoring and Oversight

RBR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab/placebo) 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 anticancer therapy
- Pregnancy

- Unequivocal radiographic evidence of disease recurrence (local recurrence, new second primary SCCHN, or distant metastasis of SCCHN), radiographic disease progression per RECIST v1.1, or symptomatic deterioration attributed to disease progression

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

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Following completion of the last treatment cycle, patients will return for a treatment discontinuation visit within 30 days of the last study dose. The visit at which tumor assessment shows recurrent or progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment in the absence unequivocal radiographic evidence of disease recurrence or progression must continue to undergo tumor assessments.

4.6.1.1 Post-Treatment Assessments

After treatment discontinuation, all patients will continue into post-treatment follow-up as outlined in the schedule of activities (see Appendix 1).

Patients who discontinue study drug (for any reason) in the absence of disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or disease progression (per RECIST v1.1) must continue to undergo radiographic assessments per schedule until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per RECIST v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. In addition, patients that continue scanning after treatment discontinuation must complete survival follow-up information and PRO assessments based on the same schedule as the tumor assessments.

After discontinuation of study treatment, survival follow-up and PRO assessments will occur approximately every 3 months or more frequently until death (unless the patient withdraws consent, or the Sponsor terminates the study). For patients with confirmed radiographic evidence of disease recurrence or progression, selected scales from the EORTC QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered at 3 months (±30 days) and 6 months (±30 days).

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits and PROs that include selected scales from the EORTC

QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered at the study site or by phone. In addition (but not instead of), study staff may also use a public information source (e.g., county records) to obtain information about survival status.

All patients (irrespective of the arm to which they are randomized) will be followed for survival and new anti-cancer therapy information (including targeted therapies and immunotherapies) and subsequent progressions, unless the patient requests to be withdrawn from survival follow-up; this request must be documented in the source documents and signed by the investigator (see Section 4.6.2). Patients should also be monitored for potential late serious adverse events and adverse events of special interest at post-treatment visits.

4.6.2 Patient Discontinuation from 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 withdrawal from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study (i.e. if the patient requests to withdraw from survival follow-up), this request must be documented in the source documents and signed by the investigator. When a patient discontinues treatment (due to any reason), the patient will still be in survival follow-up unless he or she specifies he or she wants to withdrawal from survival follow-up and this request is documented in source documents and signed by the investigator. 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

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring of patients during the study (as indicated below and in Section 4.5). See Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) for complete details regarding safety reporting for this study. An iDMC has also been incorporated into the study design to periodically review safety data (see the iDMC Charter for a detailed monitoring plan).

Administration of atezolizumab and placebo will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below (see Section 5.1.2) and in Appendix 9. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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, nephritis, *pericardial disorders,* myositis, and severe cutaneous adverse reactions. *In addition, i*mmune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis*(HLH)* Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab (see also Appendix 9).

Guidelines for managing patients who experience anticipated adverse events are provided in *Appendix 9*.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modification, Treatment Interruption, or Treatment Discontinuation

There will be no dose reduction for atezolizumab/placebo in this study.

Study drug (atezolizumab or placebo) 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 ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

If study drug is withheld for >42 days after event onset, the patient will be discontinued from study drug and followed for safety and efficacy. If the investigator believes the patient is likely to derive clinical benefit and/or there is a need for tapering of corticosteroids to 10 mg or equivalent of prednisone and the Medical Monitor is in agreement, study drug can be resumed after being withheld for >42 days with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Atezolizumab/placebo treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.2 Management Guidelines

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 9 for the management of patients who experience atezolizumab-associated IRRs and immune-mediated adverse events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, *cardiac events*, *infusion related reactions and cytokine release syndrome,* pancreatic, dermatologic, neurologic, *renal,* myositis, and meningoencephalitis events).

For cases in which management guidelines are not covered in the protocol (see Appendix 9), patients should be managed as deemed appropriate by the investigator according to best medical judgment.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 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.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis

- Hepatitis, including AST or ALT > 10× ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, CRS, influenza like *illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome (MAS)*
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the last 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 90 days after the last 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 (v4.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), 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.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 8):

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

Table 8 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

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 as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible,

avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis Versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ULN value in combination with total bilirubin $>2\times$ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ULN 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

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 SCCHN 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). The iDMC will monitor the frequency of deaths from all causes.

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Recurrence/Progression of SCCHN

Events that are clearly consistent with the expected pattern of recurrence or progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In situations in which there is no confirmation of disease recurrence or progression, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of recurrence or progression. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted.

However, every effort should be made to document recurrence or progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease recurrence or 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 recurrence or progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

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

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

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

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

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

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

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

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data to inform adverse events assessments.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events 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 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur Prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last 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 via the

electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 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.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last 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.

In addition, if the investigator becomes aware of a serious adverse event, including a fatal 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/ *Special Situations Form* using the fax number or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Atezolizumab Investigator's Brochure

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a global Phase III, multicenter, randomized, double-blind study designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of adjuvant treatment with atezolizumab compared with placebo in approximately 406 patients with locally advanced SCCHN who have not progressed after receiving definitive local therapy.

Efficacy analyses will be performed on the ITT population, with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study treatment.

Safety analyses will be performed on all randomized patients who receive any amount of the study drug, with patients grouped according to whether any atezolizumab was received (i.e., patients who receive any dose of atezolizumab will be included in the atezolizumab arm).

Hypothesis tests will be two-sided unless otherwise indicated. Details of the analyses will be provided in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

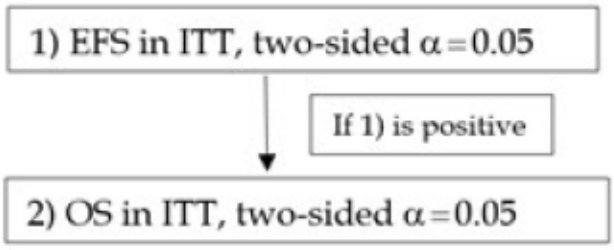
The overall type I error rate will be controlled for the two-sided test at 0.05. An overview of the α control is shown in Figure 2:

The sample size determination is based on the number of events required to demonstrate efficacy with regard to investigator-assessed EFS in the ITT population. The estimate of the number of events required is based on the following assumptions:

- Two-sided significance level of 0.05 for the EFS comparison in the ITT population
- 82% power to detect an HR of 0.65, corresponding to an improvement in median EFS from 40 months in the placebo arm to 61.5 months in the atezolizumab arm for the ITT population
- One interim futility and efficacy EFS analysis performed when approximately 80% of the total number of EFS events required for the final analysis is expected to have occurred

  Crossing boundaries for the interim efficacy and final EFS analyses will be determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.
- Dropout rate of 5% per 24 months

Figure 2 Type I Error Control Plan



EFS=event-free survival; ITT=intent-to-treat (population): OS=overall survival.

The estimate of the number of events required to demonstrate efficacy with regard to OS is based on the following assumptions:

- Two-sided significance level of 0.05 for the OS comparison in the ITT population
- 80% power to detect an HR of 0.65, corresponding to an improvement in median OS from 70 months in the placebo arm to 107.7 months in the atezolizumab arm for the ITT population
- One interim efficacy OS analysis performed at the time of the final EFS analysis, at which time approximately 121 OS events (i.e., 63% of the total number of OS events required for the final analysis) are expected to have occurred

  Crossing boundaries for the interim and final OS analyses will be determined through use of the Lan-DeMets approximation to the Pocock boundary.
- Dropout rate of 5% per 36 months

The final EFS analysis will be conducted when approximately 183 EFS events have occurred in the ITT population (expected to occur approximately 59 months after the first patient is randomized) or 65 months after the first patient is randomized, whichever occurs earlier. This number of events would allow for a minimum detectable difference (MDD) corresponding to an HR of approximately 0.74 in the ITT population.

The final OS analysis will be conducted when approximately 191 OS events have occurred in the ITT population, which is expected to occur approximately 99 months after the first patient is randomized. This number of events corresponds to a MDD in HR of approximately 0.72 in the ITT population.

With these assumptions, approximately 406 patients in total will be randomized into this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for study drug discontinuation, and reasons for study termination 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.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, race/ethnicity), stratification factors (response to definitive local therapy, HPV status, geographic region), and baseline characteristics (e.g., ECOG PS) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm for the ITT population.

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

6.4 EFFICACY ANALYSES

Efficacy analyses will be performed on the ITT population, with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study treatment.

6.4.1 Primary Efficacy Endpoint and Hypothesis Testing

The primary efficacy endpoint is EFS, as assessed by the investigator according to unequivocal radiographic evidence of disease recurrence or unequivocal radiographic evidence progression per RECIST v1.1.

EFS is defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) or death from any cause, whichever occurs first. Patients who have

not experienced disease recurrence or progression or died at the time of analysis will be censored at the time of the last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

The timing of the final investigator-assessed EFS and OS analyses is described in Section 6.1. Interim analyses are planned for both investigator-assessed EFS and OS endpoints; the details are described in Section 6.9.1.

To control the overall type I error rate for the two-sided test at 0.05, comparisons between treatment arms with respect to investigator-assessed EFS and OS will be conducted hierarchically (see Figure 2).

The primary analysis of the study will test the equality of EFS distributions in two arms:

H_0: $S_{EFS\_A}(t) = S_{EFS\_B}(t)$ versus H_1: $S_{EFS\_A}(t) \neq S_{EFS\_B}(t)$

EFS will be compared between treatment arms with the use of the stratified log-rank test. The HR for EFS for the comparison will be estimated using a stratified Cox regression model. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is less than the specified α level, then the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs the duration of EFS relative to control treatment. The 95% CI for the HR will be provided. The stratification factors will be those used during randomization, as recorded in the IxRS.

Results from an unstratified analysis may also be presented.

Kaplan-Meier methodology will be used to estimate the median EFS for each treatment arm. Brookmeyer-Crowley methodology will be used to construct the 95% CI of the median EFS for each treatment arm.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization.

See Section 6.4.1 for details on hypothesis testing for OS in the ITT population. OS will be analyzed through use of the same methods described for the EFS analysis.

6.4.2.2 Event-Free Survival Assessed by an IRF

The methodologies outlined for the investigator-assessed EFS (see Section 6.4.1) will be used for the analyses of EFS assessed by IRF.

6.4.2.3 Investigator-Assessed and IRF-Assessed Event-Free Survival at Landmark Timepoints

Investigator-assessed and IRF-assessed EFS at 1, 2, 3, and 4 years will be analyzed in the ITT population, respectively. The EFS rates will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from the Greenwood formula. The 95% CI for the difference in EFS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.4 Overall Survival at Landmark Timepoints

OS at 2, 3, and 5 years will be analyzed in the ITT population. The OS rates will be analyzed using the same methods as outlined in Section 6.4.2.3.

6.4.2.5 Patient-Reported Outcomes

The change from baseline in the five-item Physical Function and in the two-item GHS/QoL subscales of the EORTC QLQ-C30 over time while receiving treatment will be analyzed individually in the PRO-evaluable population (i.e., randomized patients who had non-missing baseline and at least one post-baseline assessments).

A score change of at least 10 points is considered clinically meaningful and will be used to define deterioration and improvement. The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001).

Mixed-effects repeated measure model will be used for comparing the Physical Function and GHS/QoL scores between treatment arms, respectively.

There is no plan to have multiplicity adjustment for PRO endpoints. Further details regarding all PRO analyses will be described in the SAP.

6.4.3 Handling of Missing Data

For EFS, patients without a date of disease recurrence or progression will be analyzed as censored observations on the date of the last tumor assessment. If no postbaseline tumor assessment is available, EFS will be censored at the date of randomization.

For OS, data for patients who are not reported as having died will be analyzed as censored observations on the date when they were last known to be alive. If no postbaseline data are available, OS will be censored at the date of randomization.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as all randomized patients who received any amount of study drug. Patients will be grouped according to whether any dose of atezolizumab was received.

Study drug exposure will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm.

Deaths reported during the study will be summarized by treatment arm.

6.6 PHARMACOKINETIC ANALYSES

Serum samples will be collected for PK analyses as outlined in Appendix 2. Serum concentrations of atezolizumab will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by cycle, as appropriate and as data allow. Individual and mean serum atezolizumab concentrations will be plotted. Atezolizumab concentration data may be subjected to population analyses to derive PK parameters such as CL, volume of distribution, and area under the curve, as warranted by the data. Potential correlations of relevant PK parameters with dose, safety, efficacy, or biomarker outcomes may be explored. These analyses may be reported separately from the Clinical Study Report. Additional PK analyses may be conducted, as appropriate, and based on the availability of data.

6.7 IMMUNOGENICITY ANALYSES

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. Summary of baseline prevalence will be based on all patients with at least one evaluable baseline ADA assessment; analysis of postbaseline incidence will be based on all patients with at least one evaluable postbaseline ADA assessment. Patients will be grouped according to treatment received.

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).

[redacted]
may be analyzed and reported via descriptive statistics.

6.8 EXPLORATORY ANALYSES

6.8.1 Subgroup Analyses

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., ECOG PS), and PD-L1 tumor expression status, the duration of investigator-assessed EFS and OS in these subgroups will be examined. Summaries of EFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median EFS and OS, will be produced separately for each level of the subgroups for the comparisons between two treatment arms.

6.8.2 Sensitivity Analyses

Sensitivity analyses will be performed to evaluate the potential impact of missing scheduled tumor assessments on the primary analysis of investigator-assessed EFS using the following two imputation rules:

- If a patient misses two or more consecutive assessments scheduled immediately prior to the date of the EFS event (disease recurrence, disease progression, or death), the patient will be censored at the last tumor assessment prior to these consecutively missed visits;
- If a patient misses two or more consecutive assessments scheduled immediately prior to the date of the EFS event, the patient will be counted as having the EFS event on the date of the first of these missing assessments. The imputation rules will be applied to patients in both treatment arms.

The impact of non–protocol-specified anti-cancer therapy on EFS may be assessed, depending on the number of patients who receive non–protocol-specified anti-cancer therapy before an EFS event. If >5% of patients receive a non–protocol-specified anti-cancer therapy before an EFS event in any treatment arm, a sensitivity analysis will be performed in which data from patients who receive non–protocol-specified anti-cancer therapy before an EFS event will be censored at the last tumor assessment date before receipt of non–protocol-specified anti-cancer therapy.

A sensitivity analysis will be performed to assess the impact of treatment discontinuation due to adverse events on the primary EFS analysis, if >5% of patients discontinue study treatment because of adverse events prior to an EFS event. In this analysis, the EFS for any patients who discontinue study treatment due to adverse events prior to an EFS event will be censored at the time of the last tumor assessment prior to treatment discontinuation.

Statistical methodologies analogous to those used in the primary analysis of investigator-assessed EFS as specified in Section 6.4.1 will be used for these sensitivity analyses.

6.8.3 Exploratory Patient-Reported Outcomes Analyses

The selected EORTC scales will be scored according to the questionnaire manuals (Fayers et al. 2001) including rules for handling missing and incomplete data at the scale level; missing data will not be imputed.

A score change of at least 10 points is considered clinically meaningful and will be used to define deterioration and improvement. The EORTC QLQ-C30 and QLQ-H&N35 data will be scored according to the EORTC scoring manual (Fayers et al. 2001).

The questionnaire completion compliance overtime will be documented in the ITT population.

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) and mean change scores will be reported in both arms at baseline, at each cycle, at end of treatment, at study discontinuation, and at survival follow-up assessments.

Change over time of treatment/disease-related symptoms as evaluated by the selected EORTC scales will be summarized by treatment arms in the PRO-evaluable population as described in Section 6.4.2.5.

A time-to-confirmed deterioration analysis of EORTC QLQ-C30 symptoms of dyspnea, appetite loss and fatigue, and EORTC QLQ-H&N35 symptoms of pain and choking will be performed and reported by treatment arm in the ITT population.

In addition, the proportion of patients with improved or decreased scores in addition to time to scores changes will be documented to best interpret treatment benefit in patient-relevant terms and presented as part of the totality of the evidence.

Further details regarding all PRO analyses will be described in the SAP. The EQ-5D-5L, including the health status VAS (Appendix 6), will be collected to inform pharmacoeconomic modeling and will not be included in the Clinical Study Report.

6.8.4 Exploratory Biomarker Analyses

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. These analyses will not be included in the Clinical Study Report.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

There is one interim futility and efficacy analysis planned for investigator-assessed EFS in this study when approximately 146 EFS events have occurred, which is approximately 47 months after the first patient is randomized. One interim efficacy analysis is planned for OS at the time of the final analysis of investigator-assessed EFS. Approximately 121 OS events are expected to have occurred at the time of the analysis.

An iDMC will be set up to evaluate safety data on an ongoing basis as well as to review the interim futility and efficacy analysis of investigator-assessed EFS. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center (iDCC). A detailed plan will be included in the iDMC Charter.

The interim futility analysis of investigator-assessed EFS will allow potential early stopping of the trial for lack of treatment benefit. The iDMC may recommend that the study be stopped for futility if the observed EFS HR >0.9 of atezolizumab arm over the control arm, which provides a probability of 74% to stop the study if the true EFS HR is 1.0 (i.e., no treatment benefit based on EFS). If there is a true treatment benefit based on EFS under the target HR of 0.65, the chance of stopping for futility is 2%. The efficacy crossing boundaries for interim efficacy and final EFS analyses will be determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary based on the actual observed number of events. If the difference in investigator-assessed EFS is statistically significant, OS will be tested. The stopping boundaries for the interim and final OS analyses will be determined through use of the Lan-DeMets approximation to the Pocock boundary based on the actual observed number of events.

Table 9 Analysis Timing and Stopping Boundary for Interim Efficacy and Final Analyses of Investigator-Assessed Event-Free Survival and Overall Survival

		Investigator-Assessed EFS		OS	
Analysis	Time from FPI (months)	Information Fraction [a] (No. of Events)	Stopping Boundary HR (p-value [b]) $\alpha=0.05$	Information Fraction [a] (No. of Events)	Stopping Boundary HR (p-value [b]) $\alpha=0.05$
EFS IA	47	80% (146)	HR: ≤ 0.688 ($p \leq 0.0242$)	—	—
EFS FA and OS IA	59	100% (183)	HR: ≤ 0.741 ($p \leq 0.0430$)	63% (121)	HR: ≤ 0.683 ($p \leq 0.0367$)
OS FA	99	—	—	100% (191)	HR: ≤ 0.723 ($p \leq 0.0252$)

EFS = event-free survival; FA = final analysis; FPI = first patient in; HR = hazard ratio; IA = interim analysis; OS = overall survival.

[a] The proportion of target number of events at each look given the total target number of events.

[b] Two-sided p-value.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final Clinical Study Report has been completed 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. 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 EU Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate Consent

Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

If the Consent Forms are revised (through an amendment or an addendum) 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.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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. The aggregate results of any conducted research will be available in accordance with the effective Roche 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.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 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.

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 170 sites globally will participate to randomize approximately 406 patients during the enrollment phase.

Randomization 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 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study as well as to review the interim analyses for EFS. Responsibilities of the iDMC and study Steering Committee will be provided in the iDMC Charter and Steering Committee Charter, respectively.

9.5 *DISSEMINATION* OF DATA AND PROTECTION OF TRADE SECRETS

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

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.

9.6 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).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003; 21:92–8.

Agrawal A, Hammond TH, Young GS, et al. Factors affecting long-term survival in patients with recurrent head and neck cancer may help define the role of post-treatment surveillance. Laryngoscope 2009;119:2135–40.

Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.

Badoual C, Combe P, Gey A, et al. PD-1 and PDL-1 expression in cancer: significance and prognostic value. Med Sci 2013;29:570–2.

Bahleda R, Braiteh FS, Balmanoukian AS, et al. Long-term safety and clinical outcomes of atezolizumab in head and neck cancer: phase Ia trial results [abstract]. Ann Oncol ESMO 2017; *A*bstract 1044O.

Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. J Clin Oncol 2017;35:1542–9.

Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:328–7.

Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Bottomley A, Tridello G, Coens C, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. Cancer 2014; 120:390–8.

Brockstein BE, Stenson KM, Song S. Overview of treatment for head and neck cancer [resource on the Internet]. UpToDate 2017 [cited:15 August 2017]. Available from: http://www.uptodate.com/contents/overview-of-treatment-for-head-and-neck-cancer?source=search_result&search=overview+of+treatment+for+head+and+neck&selectedTitle=1%7E150.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Burtness B, Bourhis JP, Vermorken JB, et al. Afatinib versus placebo as adjuvant therapy after chemoradiation in a double-blind, phase III study (LUX-Head & Neck 2) in patients with primary unresected, clinically intermediate-to-high-risk head and neck cancer: study protocol for a randomized controlled trial. Trials 2014;15:469.

Burtness B, Haddad RI, Dinis J, et al. LUX-Head and Neck 2: randomized, double-blind, placebo-controlled, phase III trial of afatinib as adjuvant therapy after chemoradiation (CRT) in primary unresected, high/intermediate-risk, squamous cell cancer of the head and neck (HNSCC) patients (pts). J Clin Oncol 2017;35:6001.

Burtness B, Haddad R, Dinis J, et al. Afatinib vs placebo as adjuvant therapy after chemoradiotherapy in squamous cell carcinoma of the head and neck: a randomized clinical trial. JAMA Oncol 2019;5:1170–80.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Campbell BH, Marbella A, Layde PM. Quality of life and recurrence concern in survivors of head and neck cancer. Laryngoscope 2000;110:895–906.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the Phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol 2016;34:3838–45.

Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994;5:521–6.

Concha-Benavente F, Srivastava RM, Trivedi S, et al. Identification of the cell-intrinsic and extrinsic pathways downstream of EGFR and IFNγ that induce PD-L1 expression in head and neck cancer. Cancer Res 2016;76:1031–43.

Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603. doi: 10.1080/19420862.2015.1136043. Epub: 26 February 2016.

Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.

[EMA] European Medicines Agency. Gudelines on the clinical evaluation of anticancer medicinal products [resource available on the Internet]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf. 5 January 2019.

Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001; 19: 1358–62.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Fayers PM, Aaronson NK, Bjordal K, et al, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

[FDA] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Clinical trial endpoints for the approval of cancer drugs and biologics guidance for industry [resource available on the Internet]. [Available from: https://www.fda.gov/media/71195/download], December 2018.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Ferris RL. Immunology and immunotherapy of head and neck cancer. J Clin Oncol 2015;33:3293–304.

Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.

Final Report of the Head and Neck Contracts Program. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Cancer 1987;60:301–11.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Forastiere AA, Shank D, Neuberg D, et al. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998;82:2270–4.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.

Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562–7.

Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709–20.

Gillison ML, Blumenschein GR, Fayette J, et al. Nivolumab (Nivo) vs investigator's choice (IC) for platinum-refractory (PR) recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN; Checkmate 141): outcomes in first-line (1L) R/M patients and updated safety and efficacy [abstract]. J Clin Oncol 2017. Abstract 6019.

Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524–48.

Grégoire V, Lefebvre JL, Licitra L, et al. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:184–6.

Harrington K, Temam S, Mehanna H, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: a phase III, randomized, double-blind, placebo-controlled study. J Clin Oncol 2015;33:4202–9.

Hecker DM, Wiens JP, Cowper TR, et al. Can we assess quality of life in patients with head and neck cancer? A preliminary report from the American Academy of Maxillofacial Prosthetics. J Prosthet Dent 2002;88:344–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540–50.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014;515:563–7.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Higgs BW, Robbins PB, Blake-Haskins JA, et al. High tumoral IFNγ mRNA, PD-L1 protein, and combined IFNγ mRNA/PD-L1 protein expression associates with response to durvalumab (anti-PD-L1) monotherapy in NSCLC patients. Eur J Cancer 2015;51(Suppl 3):S717.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Ann Rev Immunol 2008;26:677–704.

Keytruda® (pembrolizumab) U.S. Package Insert. Merck & Co., Inc. Available from: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Laramore GE, Scott CB, al-Sarraf M, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. Int J Radiat Oncol Biol Phys 1992;23:705–13.

Larkins E, Blumenthal GM, Yuan W, et al. FDA approval summary: pembrolizumab for the treatment of recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. Oncologist 2017;22:873–8.

Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013;499:214–8.

Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2021;22:450–62.

Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1/PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 2013;73:1733–41.

Machiels JP, Tao Y, Burtness B, et al. Pembrolizumab given concomitantly with chemoradiation and as maintenance therapy for locally advanced head and neck squamous cell carcinoma: KEYNOTE-412. Future Oncol 2020;16:1235–43.

Mendenhall WM, Logan HL. Human papillomavirus and head and neck cancer. Am J Clin Oncol 2009;32:535–9.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Muro K, Bang Y-J, Shankaran V, et al. Relationship between PD-L1 expression and clinical outcomes in patients (pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012. J Clin Oncol 2015;33(3 Suppl):3.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Head and neck cancers. Version 2 [resource on the Internet]. 2017 [cited: 12 July 2017]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[NCCN] National Cancer Comprehensive Cancer Network. Recommendations of the NCCN COVID 19 Vaccination Advisory Committee [resource on the Internet]. 2021 [cited: 28 May 2021]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2.

Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32:3858–66.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549–56.

Opdivo® (nivolumab) Summary of Product Characteristics. Bristol-Myers Squibb. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf.

Opdivo® (nivolumab) U.S. Package Insert. Bristol-Myers Squibb. [cited: 18 September 2017]. Available from: https://packageinserts.bms.com/pi/pi_opdivo.pdf.

O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol 2016;17:440–51.

Pignon JP, le Maître A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.

Rittmeyer A, Barlesi F, Waterkamp D, et al., for the OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Sankaranarayanan R, Masuyer E, Swaminathan R, et al. Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 1998;18: 4779–86.

Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956–65.

Seiwert TY, Haddad RI, Gupta S, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): preliminary results from KEYNOTE-012 expansion cohort [abstract]. J Clin Oncol 2015;33:abstract LBA6008.

Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer 2005;103:1843–9.

[SITC] Society for Immunotherapy of Cancer. SITC statement on SARS-CoV-2 vaccination and cancer immunotherapy [press release on the Internet]: 23 December 2020 [cited: 28 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov2-vaccination-cancer-immunotherapy.

Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963–8.

Sprangers MA, Groenvold M, Arraras JI, et al.The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14: 2756–68.

Tao Y, Auperin A, Sire C, et al. Multicenter randomized double-blind, placebo-controlled trial Gortec (Goupe Oncologie Radiotherapie Tete et Cou) 2009-01 evaluating the effect of the regenerating agent on radiodermatitis of head and neck cancer patients. Int J Radiat Oncol Biol Phys 2017;99:590–5.

Tecentriq® (atezolizumab) Summary of Product Characteristics. F. Hoffmann-La Roche. Available from: https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf.

Tecentriq® (atezolizumab) U.S. Package Insert. Genentech 2021. Available from: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.

Vokes EE, Agrawal N, Seiwert TY. HPV-associated head and neck cancer. J Natl Cancer Inst 2015;107:djv344.

Wyss A, Hashibe M, Chuang SC, et al. Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Am J Epidemiol 2013;178:679–90.

Yang J, Riella LV, Chock S, et al. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Ye Y, Li A, Liu L, et al. A group sequential Holm procedure with multiple primary endpoints. Stat Med 2013;32:1112–24.

Appendix 1
Schedule of Activities

Assessment	Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening [a]	All Cycles	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	Discontinuation [b] ≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s)	x [c]			
Pretreatment tumor tissue specimen for biomarker testing [d]	x			
Demographic data	x			
Medical history (including drugs of abuse) and baseline conditions	x			
SCCHN cancer history/tobacco use history/alcohol use history	x			
HPV status	x [e]			
Patient-reported outcomes [f]		x [g]	x	x [h]
Vital signs [i]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [j]	x		x	
Limited physical examination [k]		x [o]		
ECOG Performance Status	x	x [o]	x	
12-Lead ECG [l]	x	As clinically indicated		
Hematology [m]	x [n]	x [o]	x	
Serum chemistry [p]	x [n]	x [o]	x	

Appendix 1: Schedule of Activities (cont.)

Assessment	Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening [a]	All Cycles	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	Discontinuation [b] ≤30 Days after Last Dose	Follow-Up
Pregnancy test [q]	x [n]	x [q, o]	x	
Coagulation panel (aPTT, INR)	x [n]		x	
TSH, free T3, free T4 [r]	x	x [o, r]	x	
Viral serology [s]	x			
Urinalysis [t]	x	x [u]	x	
Serum sample for ADA assessment		See Appendix 2.		
Serum sample for PK sampling		See Appendix 2.		
Blood samples for biomarkers		See Appendix 2.		
Blood sample for RBR (optional) [v, w]		x [w]		
Tumor biopsy (optional) [x]		At the time of initial radiographic confirmation of disease recurrence or progression (preferred) and/or any time during treatment or survival follow-up (at investigator's discretion) [x]		
Tumor assessments	x [y]	Every 9 weeks following C1D1 (±7 days; at approximately every three cycles) in the first 2 years; every 12 weeks (±10 days) during Year 3; and every 16 weeks for Years 4 and 5 (±10 days), and annually thereafter at the investigator's discretion until death, unequivocal radiographic evidence of disease recurrence (local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or radiographic progression per RECIST v1.1, loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. [z]		

Assessment	Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening [a]	All Cycles	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	Discontinuation [b] ≤30 Days after Last Dose	Follow-Up
Concomitant medications [aa]	x	x	x	
Adverse events [bb]	x	x	x	
Study drug administration [cc]		x		
Survival follow-up and anti-cancer treatment				x [dd]

ADA=anti-drug antibody; C=cycle; C1D1=Cycle 1, Day 1; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HPV=human papillomavirus; IHC=immunohistochemistry; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; QLQ-C30=Quality of Life–Core 30 Questionnaire; QLQ-H&N35=Quality of Life–Head and Neck, Module 35 Questionnaire; QoL=quality of life; RBR=Research Biosample Repository; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; VAS=Visual Analog Scale.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used (except where otherwise specified); such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows recurrent or progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before, but no more than 56 days prior to initiation of study treatment.

[d] A pretreatment tumor tissue (archival or freshly obtained) sample must be submitted within 4 weeks after randomization. This specimen must be accompanied by the associated pathology report. It is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or a minimum of 15 serial, freshly cut, unstained slides be submitted. If resection specimen is not available, patients can submit tumor specimens from a core needle biopsy collected prior to study randomization. If patient is not a surgical candidate or tissue is not available from resection or biopsy, any representative tissue sample can be submitted. See Section 4.5.6 for details.

[e] HPV status of tumor tissue determined by any of the following methods: p16 IHC, in situ hybridization, or polymerase chain reaction–based assay. If HPV status by p16 IHC, in situ hybridization, or polymerase chain reaction–based assay is unknown, archival tumor tissue or freshly collected tumor tissue must be tested at screening.

[f] The PRO questionnaires, including selected scales from the EORTC questionnaires (e.g., QLQ-C30 and QLQ-H&N35) and the EQ-5D-5L in its entirety (including the VAS), will be completed by the patients at the investigational site on paper. All PRO questionnaires are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) involving communication with the clinical staff (e.g., discussion of tumor progression) that could bias patients' rating of their health status (symptoms, signs, functioning, or QoL) to ensure that the validity of the assessment is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. Reasons for non-completion should be recorded on the eCRF.

[g] It is imperative that the selected scales from the EORTC questionnaires and the EQ-5D-5L in its entirety be completed on Day 1 of Cycle 1 to have a baseline. Each questionnaire will be completed on Day 1 of each cycle, at the treatment discontinuation visit, and at unscheduled visits as clinically indicated. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias a patient's responses.

[h] After discontinuation of the treatment and in the absence of unequivocal radiographic evidence of disease recurrence or progression, selected scales from the EORTC QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered at the same schedule as the tumor assessments until disease recurrence or progression, at the study site or by telephone. After the confirmation of unequivocal radiographic evidence of disease recurrence or progression, selected scales from the EORTC QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered over the telephone or during clinic *visits* at 3 months (±30 days) and 6 months (±30 days) by site personnel.

[i] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure in the seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[j] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Ongoing use of tobacco (smoking and smokeless) must also be recorded. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Complete physical examinations are defined in Section 4.5.3.

[k] Perform a limited, symptom-directed examination at every cycle and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Ongoing use of tobacco (smoking and smokeless) must also be recorded. Limited physical examinations are defined in Section 4.5.3.

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

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Specified screening laboratory test results must be obtained prior to randomization and within 14 days prior to initiation of study treatment.

[o] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, laboratory assessments do not have to be repeated at C1D1. At all cycles subsequent to C1D1, laboratory assessments, ECOG Performance Status, and limited physical examination must be performed within 96 hours prior to administration of drug.

[p] Chemistry panel (serum) includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[q] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1 of Cycle 1. Either urine or serum pregnancy tests must be performed within 96 hours prior to administration study drug at every cycle during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 1, 5, 9, etc.).

[s] At screening and prior to randomization, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[t] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[u] Urinalysis should be performed as clinically indicated during study treatment.

[v] Blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at baseline (predose on Day 1 of Cycle 1). However, if the RBR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[w] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[x] Biopsy at radiographic disease recurrence or progression should be performed within 40 days after progression or recurrence or prior to the next anti-cancer therapy, whichever is sooner. Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.9 for tissue sample requirements.

[y] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck region. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI with contrast scans of the abdomen and head and neck region must be performed. All measurable and non-measurable lesions should be assessed and documented at screening. If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from the Medical Monitor.

[z] The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used at screening must be used for subsequent tumor assessments. Imaging of the head and neck region and chest must be performed at every scheduled tumor assessment. Imaging of the abdomen and bone must be performed as clinically indicated, and imaging of the abdomen must also be done upon disease recurrence or progression in the head and neck and/or chest. All measurable and non-measurable lesions should be re-assessed at each subsequent timepoint. Progression of patients with evidence of residual disease at baseline (as assessed by screening scans) will be assessed by the investigator using RECIST v1.1. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Disease recurrence in patients with no evidence of disease at baseline (as assessed by screening scans) will be determined by the investigator based on unequivocal radiographic evidence of recurrence (local recurrence, new second primary SCCHN lesion, or development of distant metastasis). At any time that disease recurrence or progression is clinically suspected, protocol required imaging must be performed expeditiously outside the schedule timepoints, even if not mandated in the schedule of activities. In cases of equivocal evidence of recurrence or progression, recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated. Tumor assessments will continue regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started) until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per RECIST v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

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

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last 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. 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.

[cc] Patients should receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 4 days after randomization. The initial infusion of study drug will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[dd] After discontinuation of 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. In addition (but not instead of), study staff may also use a public information source (e.g., county records) to obtain information about survival status. Patients who have discontinued study drug (for any reason) in the absence of disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or disease progression (per RECIST v1.1) must complete survival follow-up on the same schedule as the radiographic assessments until the protocol-defined criterion for ending radiographic assessments is met. After both treatment and radiographic assessments are discontinued, survival follow-up must occur approximately every 3 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator. If a patient withdraws from the study (i.e. survival follow-up), the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Fluid Samples for All Enrolled Patients in Arms A and B

Visit	Timepoint	Sample Type
Day 1 of Cycle 1	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and blood [a]) • Blood sample for RBR (optional) [b]
	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 4	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 8	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 16	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA=anti-drug antibody; PK=pharmacokinetic; RBR=Research Biosample Repository.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] If this blood sample is not collected during the Day 1, Cycle 1 visit, it may be collected at any other visit during the conduct of the clinical study.

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

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

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

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or 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").

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with 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, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

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

All lesions (or sites of disease) not selected as target lesions (measurable or 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, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

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

CRITERIA FOR NON-TARGET LESIONS

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

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

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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

Patients with Non-Measurable Disease Only

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

NEW LESIONS

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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

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

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

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 and Table 2.

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.

REFERENCE

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

Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30); Modified

EORTC QLQ-C30 (Modified)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
8.	Were you short of breath?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
18.	Were you tired?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
Quality of Life–Head and Neck Cancer, Module 35 Questionnaire (QLQ-H&N35); Modified

EORTC QLQ-H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4

During the past week:		No	Yes
61.	Have you used painkillers?	1	2

Appendix 6
EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

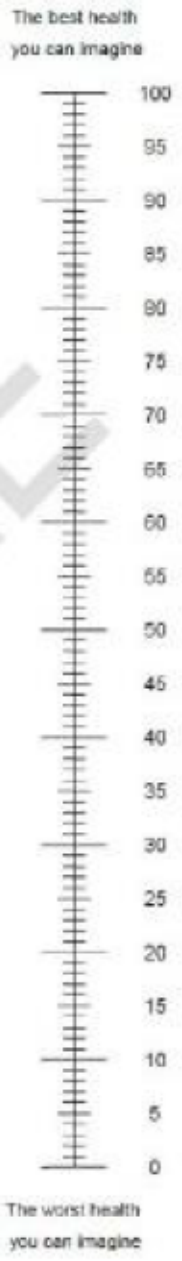
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Appendix 7
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor *is available to advise on any uncertainty* over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome	• Crohn disease • Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 8
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

- Stop the study treatment infusion.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 9
Management of Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab 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.

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 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.

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

- *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.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. Resumption of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the immune-mediated event. *The decision to re-challenge p*atients with atezolizumab

should be based on the investigator's assessment of the benefits and risk and documented by the investigator. The Medical Monitor is available to advise as needed.

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 also 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. *Coronavirus 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

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

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

BAL=bronchoscopic alveolar lavage.

[a] *Atezolizumab* may be withheld for a longer period of time (i.e., >12 weeks after eventonset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

HEPATIC EVENTS

Patients eligible for study treatment 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 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.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT=liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

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

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day oral prednisone. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

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

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor.[c] • Refer patient to GI specialist for evaluation and confirmat*ory* biopsy. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 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.

Table 4 Management Guidelines for Endocrine Events

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

IMMUNE-MEDIATED MYOCARDITIS

Management guidelines for cardiac events are provided in Table 6.

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., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, 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 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 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 related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), 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, transthoracic echocardiogram, 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 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

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

Event	Management
Immune-mediated myocarditis, Grade 1	• *Refer patient to cardiologist.* • *Initiate treatment as per institutional guidelines.*
Immune-mediated myocarditis, Grades 2-4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* as appropriate. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab 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. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab 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 7.

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

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

Event	Management
Grade 1 [a] fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
Grade 2 [a] *Fever* [b] with hypotension not requiring vasopressors **and/or** *Hypoxia* requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact *the* Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

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

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

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up 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 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

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 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10, *with specific guidelines for myelitis provided in* Table 11.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *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	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – *If event resolves to Grade 1 or better, resume atezolizumab.* [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis*. Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

Table 10 Management Guidelines for Neurologic Disorders (cont.)

Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

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

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

Table 11 Management Guidelines for Immune-Mediated Myelitis

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

IMMUNE-RELATED 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 12.

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

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

RENAL EVENTS

Eligible patients must have adequate renal function, and 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 13

Table 13 Management Guidelines for Renal Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. *The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* These guidelines are per the Atezolizumab Investigator's Brochure and the defined window for treatment discontinuation in Section 5.1.2.1 supersedes these and should be followed accordingly.

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

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

IMMUNE-MEDIATED 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 increase), and

imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

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

Table 14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Recurrent Grade 3, and Grade 4 [d]	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c] • *Refer patient to rheumatologist or neurologist.* • *Initiate treatment as per institutional guidelines.* • *Respiratory support may be required in more severe cases.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.* • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.*

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

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

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

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

[d] *The highest grade described for myositis in CTCAE v4.0 is Grade 3. However, if the investigator assesses the event as more severe than Grade 3, please follow the guidelines provided above for the management of Grade 4 myositis as defined in NCI CTCAE v5.0.*

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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 < 100×10^9/L (100,000/μL)
  - ANC < 1.0×10^9/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 interleukin (IL2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/μL)
  - AST 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti-programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502-4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190-6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465-77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481-9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323-35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908-14.

Appendix 10
Investigational Medicinal Product (for Use in European Economic Area and United Kingdom)

Table 1 Investigational Medicinal Product Designations for European Economic Area and United Kingdom

Product Name	*IMP Designation*	*Marketing Authorization Status in EEA and UK*	*Used within Marketing Authorization*
Atezolizumab (RO5541267)	*IMP (test product)* [a]	*Authorized*	*No* [b]
RO5541267	*IMP (placebo)*	*Not applicable*	*Not applicable*

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

[a] *Atezolizumab is considered to be an IMP test product.*

[b] *Atezolizumab is approved in the EEA for other indications but not for the treatment of squamous cell carcinoma of the head and neck (SCCHN).*

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