Official Title: A Phase III, Multicenter, Randomized, Open-Label, Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Atezolizumab Given in Combination With Cabozantinib Versus Docetaxel Monotherapy in Patients With Metastatic Non-Small Cell Lung Cancer Previously Treated With an Anti-PD-L1/PD-1 Antibody and Platinum-Containing Chemotherapy

NCT Number: NCT04471428

Document Date: Protocol Amendment Version 5: 22-March-2023

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS DOCETAXEL MONOTHERAPY IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH AN ANTI–PD-L1/PD-1 ANTIBODY AND PLATINUM-CONTAINING CHEMOTHERAPY**
PROTOCOL NUMBER:	GO41892
VERSION NUMBER:	5
TEST PRODUCTS:	Atezolizumab (RO5541267) and cabozantinib (XL184)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 146261 EudraCT Number: 2020-000100-11 NCT Number: NCT04471428
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 Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
5	See electronic date stamp on the final page of this document	France	4	To be determined
4	10 March 2022	France	3	25 March 2022
3	18 March 2021	France	2	26 April 2021
2	29 June 2020	France	1	14 October 2020
1	27 February 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol GO41892, Version 5, has been amended primarily to update the adverse event management guidelines to align with the recent Atezolizumab Investigator's Brochure, Version 19, and Cabozantinib Investigator's Brochure, Version 18.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Two newly approved indications for cabozantinib have been added to align with the Cabozantinib Investigator's Brochure, Version 18 (Section 1.3).
- A note has been added that the completion of patient-reported outcome (PRO) questionnaires will no longer be required after the final overall survival (OS) analysis (Sections 3.1, 4.5.9, 4.6.1.1, and Appendix 1).
- The duration of follow-up after the completion of final OS analysis has been specified as 6 months after patient's last dose of study treatment (Sections 3.1, 4.5.6, 4.6.1.1, and Appendix 1).
- The end-of-study definition has been updated to include the additional criteria of when the last data point required for safety follow-up has been received (if it occurs later than the required number of deaths for the final analysis OS), and the last patient's last visit has occurred. Patients may continue on study treatment until the development of progressive disease, unacceptable toxicity, patient consent withdrawal, or Sponsor's decision to terminate the study, whichever occurs first. The Sponsor will provide a written notification to investigators in the event that the study has terminated and the investigators, in consultation with the Medical Monitor, may offer suitable patients with potential enrollment to the continued access program or another study for continued access to study treatment (Section 3.2).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in Medical Dictionary for Regulatory Activities (Section 4.1.2 and Appendix 4).
- Text has been added to clarify that the number of pharmacokinetic (PK) and anti-drug antibody (ADA) samples may be reduced or sample collection may cease altogether based on emerging safety, activity, or efficacy data. These collected samples may not be analyzed if not warranted. Furthermore, after final OS analysis is conducted, the Sponsor may decide to no longer collect additional biomarker samples. The existing collected samples may still be used for exploratory analysis. (Section 4.5.7, and Appendices 1 and 2).
- 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 to include pericardial disorders, myelitis, and facial paresis. In addition, hemophagocytic lymphohistiocytosis (HLH) has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.1).

- The list of identified risks for cabozantinib has been revised to include venous and arterial thrombotic events, angioedema, and musculoskeletal disorders (Section 5.1.2).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- Guidance has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent. Autoimmune myelitis has also been added to the table of autoimmune diseases (Appendix 4).
- The adverse event management guidelines for risks associated with atezolizumab have been updated to align with the Atezolizumab Investigator's Brochure, Version 19, as well as Addendum 1 and 2 to the Atezolizumab Investigator's Brochure, Version 19. Management guidelines for pericardial disorders, myelitis, and facial paresis have been included, and HLH has been updated from a potential risk to an identified risk (Appendix 6).
- The adverse event management guidelines for risks associated with cabozantinib have been updated to align with the Cabozantinib Investigator’s Brochure, Version 18 (Appendix 7).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS DOCETAXEL MONOTHERAPY IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH AN ANTI–PD-L1/PD-1 ANTIBODY AND PLATINUM-CONTAINING CHEMOTHERAPY**
PROTOCOL NUMBER:	GO41892
VERSION NUMBER:	5
TEST PRODUCT:	Atezolizumab (RO5541267) and cabozantinib (XL184)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ATEZOLIZUMAB GIVEN IN COMBINATION WITH CABOZANTINIB VERSUS DOCETAXEL MONOTHERAPY IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH AN ANTI–PD-L1/PD-1 ANTIBODY AND PLATINUM-CONTAINING CHEMOTHERAPY**
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 146261 EudraCT Number: 2020-000100-11 NCT Number: NCT04471428

STUDY RATIONALE

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab when given in combination with cabozantinib (Atezo + Cabo) compared with docetaxel monotherapy in patients with metastatic non-small cell lung cancer (NSCLC), with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinas (ALK) translocation, who have progressed on prior treatment with both anti-PD-L1/PD-1 antibody and platinum-containing chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

OBJECTIVES AND ENDPOINTS

EFFICACY OBJECTIVES

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Overall survival (OS), defined as the time from randomization to death from any cause

SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoints:

- Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumor, Version 1.1. (RECIST v1.1), or death from any cause (whichever occurs first)
- Confirmed objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of response (DOR) for patients with confirmed ORR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)

- Time to confirmed deterioration in patient–reported Physical Function (PF) and global health status (GHS) as measured by the corresponding scores from the European Organisation for the Research and Treatment of Cancer Quality of Life–Core 30 (EORTC QLQ-C30)
- PFS rates assessed by the investigator at 6 months and at 1 year
- OS rates at 1 and 2 years

SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Incidence and severity of adverse events with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of Atezo + Cabo on the basis of the following endpoints:

- Serum concentration of atezolizumab at specified timepoints
- Plasma concentration of cabozantinib at specified timepoints

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to Atezo + Cabo on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after treatment

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab given in combination with cabozantinib compared with docetaxel monotherapy in patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* translocation, who have progressed following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially.

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

Phase:	*Phase III*	***Population Type:***	*Adult patients*
Control Method:	*Active comparator*	***Population Diagnosis or Condition:***	*Metastatic non-small cell lung cancer*
Interventional Model:	*Parallel group*	***Population Age:***	*≥18 years*
Test Compound{s}:	*Atezolizumab and cabozantinib*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Docetaxel*	***Study Intervention Assignment Method:***	*Randomization and stratification*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*Approximately 350*

In the experimental arm: Atezolizumab and cabozantinib treatment will continue until unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). During study treatment, patients who meet criteria for disease progression per RECIST v1.1 and show evidence for clinical benefit may continue atezolizumab and/or cabozantinib treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom other treatment options/standard therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are atezolizumab, cabozantinib, and docetaxel.

TEST PRODUCTS (INVESTIGATIONAL DRUG)

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

Cabozantinib will be administered orally, once a day at a dose of 40 mg (2×20-mg tablets) on Days 1–21 of each cycle.

COMPARATOR

Docetaxel will be administered by IV infusion at a starting dose of 75 mg/m^2 every 3 weeks according to the locally approved label.

END OF STUDY

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

- *The required number of deaths for the final analysis of OS has been observed or the last data point required for safety follow-up is received, whichever occurs later.*
- *The last patient's last visit has occurred.*

In addition, the Sponsor may decide to terminate the study at any time and provide a written notification to investigators. Patients may continue study treatment until the development of progressive disease, unacceptable toxicity, patient consent withdrawal, or Sponsor's decision to terminate the study, whichever occurs first. If the Sponsor decides to end the study, patients still receiving study treatment may be offered participation in the continued access program or enrollment into another study for continued access to study treatment, if, in the opinion of the investigator and in consultation with the Medical Monitor, the patient would potentially benefit from continuing therapy and the patient cannot reasonably obtain treatment outside of the program.

LENGTH OF STUDY

The approximate total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 47 months.

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
ALK	anaplastic lymphoma kinase
AUC	area under the plasma concentration–time curve
COPD	chronic obstructive pulmonary disease
CR	complete response
CRS	cytokine-release syndrome
CSR	Clinical Study Report
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
DTC	*differentiated thyroid carcinoma*
DVT	deep vein thrombosis
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC IL46	European Organisation for Research and Treatment of Cancer Item List 46
EORTC IL17	European Organisation for Research and Treatment of Cancer Item List 17
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
HBV	hepatitis B virus
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
iDMC	independent Data Monitoring Committee
IFN	interferon
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat (analysis or population)
IV	*intravenous*
IxRS	interactive voice or web-based response system
LMWH	low-molecular-weight heparin
MET	mesenchymal–epithelial transition
MN	mobile nursing
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
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
PCR	polymerase chain reaction
PD	progressive disease
PD(L)1	PD-L1/PD-1
PF	Physical Function
PFS	progression-free survival
PK	pharmacokinetic
PPE	palmar-plantar erythrodysesthesia
PR	partial response

Abbreviation	Definition
PRO	patient-reported outcome
Q3W	every 3 weeks
QD	once a day
QLQ-C30	Quality of Life–Core 30 Questionnaire
QLQ-LC13	Quality of Life–Lung Cancer 13-Item Questionnaire
QOD	every other day
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RAI	*radioactive iodine*
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RF	Role Function
RTK	receptor tyrosine kinase
SAP	Statistical Analysis Plan
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SE	standard error
SITC	Society for Immunotherapy of Cancer
SD	stable disease
SmPC	Summary of Product Characteristics
T3	free triiodothyronine
TIA	*transient ischemic attack*
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor–α
TPS	tumor proportion score
ULN	upper limit of normal
USPI	U.S. Package Insert
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON NON–SMALL CELL LUNG CANCER

Lung cancer is one of the most frequently diagnosed cancers worldwide and is also the leading cause of cancer deaths in developed countries. In the United States, it was estimated that 228,150 new cases (116,440 in men and 111,710 in women) were diagnosed in 2019, while more than 142,670 deaths will occur (76,650 in men and 66,020 in women; Torre et al. 2016; Seigel et al. 2019). In Europe, 470,000 new cases of lung cancer in 2018 have been estimated (311,800 in men and 158,200 in women), while 387,900 deaths were expected to occur (267,300 in men and 120,600 in women; Ferlay et al. 2018).

Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 84% of all lung cancer cases (Howlader et al. 2015). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma. Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for NSCLC is 23% but drops to as low as 6% for metastatic NSCLC (Cancer.Net 2019). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

Treatment options for patients with Stage IV NSCLC are informed by the presence or absence of genetic alterations. Current treatment guidelines recommend testing for the genetic abnormalities including epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase *(ALK)* rearrangements, *ROS1* rearrangements, and *NTRK* fusions and *BRAF* mutations; as well as the presence or absence of PD-L1 expression on tumor or tumor-infiltrating immune cells. There are several other targets that are being tested for, including mesenchymal-epithelial transition (MET) alterations, rearranged during transfection (RET) rearrangements, and *HER2* mutation. The introduction of tyrosine kinase inhibitor (TKI)-based therapy has transformed treatment approaches for many of these patients.

Platinum-containing chemotherapy with or without vascular endothelial growth factor (VEGF) targeted therapy (bevacizumab) has been the standard of care front-line therapy in patients with advanced NSCLC who do not have genetic markers that can be selectively targeted. Recently, immune checkpoint inhibitors (ICIs) targeting the PD-L1/PD-1 signaling pathway have become a new treatment choice in patients with

metastatic NSCLC by improving overall survival (OS) and progression-free survival (PFS) compared with standard chemotherapy (Reck et al. 2016; Gandhi et al. 2018; Socinski et al. 2018; Reck et al. 2019). Currently, several antibody plus chemotherapy combinations are approved as first-line treatment of patients with metastatic nonsquamous NSCLC: 1) atezolizumab (anti–PD-L1 antibody) in combination with bevacizumab, paclitaxel, and carboplatin; 2) atezolizumab in combination with carboplatin and paclitaxel protein-bound; and 3) pembrolizumab (anti–PD-1 antibody) in combination with pemetrexed and platinum-containing chemotherapy (Tecentriq® U.S. Package Insert [USPI] and European Medicines Agency [EMA] Summary of Product Characteristics [SmPC]; Keytruda® USPI and EMA SmPC). Additionally, pembrolizumab in combination with carboplatin and either paclitaxel or paclitaxel protein-bound is approved as first-line treatment of patients with metastatic squamous NSCLC (Keytruda USPI and EMA SmPC). Pembrolizumab is also approved as a monotherapy for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 with no *EGFR* or *ALK* translocations (Keytruda USPI and EMA SmPC).

In addition, several anti–PD-L1/PD-1 antibodies have been approved by regulatory agencies as a single-agent therapy in patients with NSCLC after prior platinum-containing therapy. These include atezolizumab (Tecentriq USPI and EMA SmPC), nivolumab (Opdivo® USPI and EMA SmPC), and pembrolizumab (Keytruda USPI and EMA SmPC). The use of an anti–PD-L1/PD-1 antibody earlier in the treatment paradigm has created a high unmet medical need for anti–PD-L1/PD-1 ICI and platinum-refractory patients in second and third lines of therapy.

For patients who progress on an anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy given sequentially or in combination, additional treatment options include single-agent chemotherapy, such as docetaxel and pemetrexed (Planchard et al. 2018). The activity of single-agent chemotherapy following platinum-containing first-line therapy is modest with objective response rate (ORR) of $<10\%$ and median PFS and OS ranging from 2–3 months and 8–9 months, respectively (Hanna et al. 2004; Garon et al. 2014). Although higher response rates have been reported for salvage chemotherapy following anti–PD-L1/PD-1 ICI therapy, the median PFS and OS appear to be similar in anti–PD-L1/PD-1 ICI-pretreated and anti–PD-L1/PD-1 ICI-naive patients who have previously received platinum-containing chemotherapy (Grigg et al. 2017; Schvartsman et al. 2017; Park et al. 2018). Another treatment option for patients who progress on or after platinum-containing treatment is the combination of an anti-VEGF receptor 2 (VEGFR2) antibody, ramucirumab, with docetaxel. Compared with docetaxel alone, this combination demonstrated a modest increase in median PFS (4.5 vs. 3.0 months) and median OS (10.5 vs. 9.1 months; Garon et al. 2014).

1.2 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.

As noted above, atezolizumab is approved as a combination therapy with either bevacizumab, paclitaxel, and carboplatin; or with carboplatin and paclitaxel protein-bound for the first-line treatment of patients with metastatic nonsquamous NSCLC (Tecentriq USPI, Tecentriq EMA SmPC). Atezolizumab monotherapy is approved as first-line treatment for patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained $\geq$50% of tumor cells [TC $\geq$50%] or PD-L1 stained tumor-infiltrating immune cells [IC] (Tecentriq USPI). Atezolizumab monotherapy is also approved for patients who have disease progression during or following platinum-containing chemotherapy (Tecentriq USPI, Tecentriq EMA SmPC). Additionally, atezolizumab is also approved for the treatment of urothelial carcinoma, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.3 BACKGROUND ON CABOZANTINIB

Cabozantinib (XL184) is a potent, orally bioavailable inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization, including the VEGFR2, MET, and RET. Cabozantinib targets also include TYRO3, AXL, and MER (TAM family kinases) and are implicated in promoting suppression of an anti-tumor immune response. Preclinical studies (Kwilas et al. 2014; Song et al. 2015; Lu et al. 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al. 2014) suggest that cabozantinib promotes an immune-permissive environment, which might present an opportunity for synergistic effects from combination treatment with ICIs independent of PD-L1 expression.

Cabozantinib (60 mg, tablets) is approved as single agent for patients with advanced renal cell carcinoma (RCC) and in combination with nivolumab as first-line treatment for patients with advanced RCC (Cabometyx® USPI), for adult patients with advanced RCC

after prior VEGF-targeted therapy or treatment-naïve adult patients with intermediate or poor risk RCC (Cabometyx EMA SmPC), and for patients with hepatocellular carcinoma who have previously been treated with sorafenib (Cabometyx USPI and EMA SmPC). In addition, cabozantinib (140 mg, capsules) is approved for patients with progressive, metastatic medullary thyroid cancer (Cometriq® USPI and EMA SmPC). The capsule and tablet formulations are not bioequivalent or interchangeable.

Cabozantinib (40 mg or 60 mg tablets, depending on body surface area) is also approved for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine (RAI)-refractory or ineligible (Cabometyx USPI). Additionally, the use of cabozantinib is approved in the European Union and other regions as a second-line treatment in RAI-refractory DTC in adult patients.

Cabozantinib once a day (QD) has been evaluated as a single agent and in combination in several early stage clinical trials in ICI-naive patients with advanced NSCLC. In an open-label, randomized Phase II study sponsored by National Cancer Institute (NCI), 125 patients with nonsquamous NSCLC without *EGFR* genetic alterations received cabozantinib (60 mg QD), erlotinib (150 mg QD), or both agents in combination (erlotinib 150 mg QD + cabozantinib 40 mg QD) as second- or third-line (post-platinum-containing chemotherapy) treatment (Neal et al. 2016). Compared with erlotinib alone, the primary endpoint of PFS was significantly improved in patients receiving cabozantinib as single agent (4.3 vs. 1.8 months; hazard ratio [HR] = 0.39; p = 0.0003) and in combination with erlotinib (4.7 vs. 1.8 months; HR = 0.37; p < 0.0003). The estimated median OS for patients treated with cabozantinib alone was 9.2 months (95% CI: 5.1 to 15.0), for cabozantinib with erlotinib was 13.3 months (95% CI: 7.6 to NR), and for erlotinib alone was 5.1 months (95% CI: 3.3 to 9.3). The ORR for patients treated with cabozantinib alone was 11%. Notably, progression as best response was reported for 23%–24% for patients treated with cabozantinib alone or in combination with erlotinib, and 66% for patients treated with erlotinib alone. The most common Grade 3 or 4 adverse events for single-agent cabozantinib were hypertension (25%), fatigue (15%), oral mucositis (10%), diarrhea (8%), and thromboembolic events (8%). One death due to respiratory failure assessed as possibly related to study drug occurred in the cabozantinib arm, and one death due to pneumonitis assessed as related to either study drug or the combination occurred in the erlotinib plus cabozantinib arm.

In a Phase II randomized discontinuation trial in 526 patients across 9 disease cohorts, 60 patients with advanced NSCLC of nonsquamous (n = 43) or squamous cell (n = 17) histology received cabozantinib 100 mg QD as a single agent (Schöffski et al. 2017; Hellerstedt et al. 2019). The ORR at Week 12 (primary endpoint) was 10% in the NSCLC cohort, 6 patients had a confirmed partial response (PR), and no patients had a complete response (CR). Overall disease-control rate (ORR + stable disease [SD]) at

Week 12 was 38%. Tumor regression was observed in 30 of 47 patients (64%) with at least one postbaseline radiographic tumor assessment. Median PFS during the randomized stage was 2.4 months for the cabozantinib arm (median PFS during the entire treatment period from the start of the study was 4.2 months for all treated patients). The most frequently reported Grade 3 or 4 adverse events were fatigue (13%), palmar-plantar erythrodysesthesia [PPE] (10%), diarrhea (7%), hypertension (7%), and asthenia (5%). One treatment-related Grade 5 hemorrhage was reported; however, based on a retrospective review of the baseline tumor assessment, this patient should have been excluded from the study at screening as there was a tumor mass infiltrating the pulmonary artery, which was one of the exclusion criteria.

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

1.4 ONGOING CLINICAL STUDY WITH ATEZOLIZUMAB AND CABOZANTINIB

Cabozantinib in combination with atezolizumab is currently being evaluated in a multi-cohort Phase Ib study in patients with locally advanced or metastatic solid tumors (COSMIC-021; NCT03170960). In the dose-escalation portion of this study, 12 patients with treatment-naive advanced RCC were treated at 2 dose levels of cabozantinib (6 patients each at 40 mg and 60 mg QD) with atezolizumab administered at 1200 mg intravenously (IV) every 3 weeks (Q3W) (Agarwal et al. 2018). The ORR at the 40 mg QD level was 50% (3 of 6 patients), while at the 60 mg QD level it was 83% (5 of 6 patients). There were no dose-limiting toxicities (DLTs) or serious adverse events in either dose cohort. Most adverse events, including immune-mediated adverse events, were Grade 1 or 2 in severity. There were 3 patients (25%) who experienced Grade 3 immune-mediated adverse events (one event each of ALT increased, AST increased, GGT increased, lipase increased, and myositis). Other Grade 3 adverse events included five events of hypertension, two events each of diarrhea and hypophosphatemia, and one event each of lymphopenia, pulmonary embolism, nephritis, and hyperglycemia. All adverse events were manageable by dose modifications including dose reductions and dose delays as well as supportive care. There were no Grade 4 or 5 adverse events.

Because of a more favorable safety profile of the 40-mg cabozantinib dose level over a prolonged time on study treatment with less frequent dose reductions and encouraging preliminary efficacy, the cabozantinib dose of 40 mg QD combined with atezolizumab at 1200 mg Q3W was selected by the Cohort Review Committee as the recommended dose for expansion stage in multiple solid tumor expansion cohorts in the COSMIC-021 study. One expansion cohort (Cohort 7) is currently enrolling patients with Stage IV nonsquamous NSCLC who have radiographically progressed on or after treatment with one prior anti–PD-1 or anti–PD-L1 ICI and platinum-containing chemotherapy for

metastatic disease. This cohort has completed initial enrollment of 30 patients, and per protocol, has been allowed to enroll up to 50 additional patients.

As of 21 August 2019, 33 patients have been enrolled and treated in the expansion Cohort 7, of whom 27 patients were evaluable for efficacy. Preliminary clinical activity is encouraging: 8 patients with a best response of PR (6 confirmed PRs and 2 unconfirmed PRs) and 15 patients with a best response of SD. The most common adverse events of any grade regardless of causality in the 33 patients who were evaluable for safety comprised diarrhea (45%), fatigue (33%), constipation (30%), decreased appetite (27%), asthenia (24%), nausea (24%), hypertension (21%), and vomiting (21%). Grade 4 adverse events comprised neutrophil count decrease (n = 1), hyponatremia (n = 1), dehydration (n = 1), atrial thrombosis (n = 1), and white blood cell count decreased (n = 1). There were five serious adverse events considered to be related to study treatment (Grade 3 nausea, Grade 3 PPE, Grade 4 atrial thrombosis, Grade 4 dyspnea and subsequent death in one patient). Grade 5 adverse events observed were disease progression (n = 2), death (n = 2), completed suicide (n = 1), sepsis secondary to disease progression (n = 1), and general physical health deterioration (n = 1). Only one of these Grade 5 events (death) is considered related to study treatment by the investigator. This patient had Grade 5 events considered related to atezolizumab (interstitial lung disease, myocarditis, and death).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.5.1 Study Rationale

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 use of anti–PD-L1/PD-1 antibody in the first-line setting has shifted the treatment landscape creating a high unmet medical need for anti–PD-L1/PD-1 ICI-refractory patients in second and third lines of therapy.

For patients who progress on anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy given sequentially or in combination, additional treatment options include single-agent chemotherapy, such as docetaxel and pemetrexed (NCCN 2019; European Society for Medical Oncology [ESMO] guidelines for metastatic NSCLC, Planchard et al. 2018). Given the modest activity of these agents, there is a significant unmet need for novel treatment options in patients with NSCLC who have progressed on or after prior platinum-containing chemotherapy and anti–PD-L1/PD-1 therapies.

The combination of atezolizumab and cabozantinib has shown encouraging preliminary clinical activity in patients with Stage IV NSCLC who have radiographically progressed

on or after treatment with one prior anti-PD-1 or anti-PD-L1 ICI and platinum-containing chemotherapy for metastatic disease (see Section 1.4).

This is a Phase III, multicenter, randomized, open-label study to evaluate the efficacy and safety of atezolizumab given in combination with cabozantinib versus docetaxel monotherapy, in patients with metastatic NSCLC who have progressed following prior treatment with anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy.

Evaluation of single-agent cabozantinib is being performed within the Phase Ib study (COSMIC-021), in which a single-agent cabozantinib cohort is enrolling a similar patient population as this Phase III study. This allows for an evaluation of the contribution of the cabozantinib component of the combination

1.5.2 Overall Benefit–Risk Assessment

There is a significant unmet need in patients with metastatic NSCLC who have progressed following prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody. Currently, single-agent docetaxel is the most frequently used treatment option available to these patients.

This randomized, open-label, Phase III study evaluates the efficacy and safety of atezolizumab in combination with cabozantinib compared with docetaxel monotherapy in patients with metastatic NSCLC who have progressed on prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody. Preliminary clinical data with the combination of these two agents in the NSCLC cohort (Cohort 7) in the ongoing Phase Ib study (COSMIC-021) have shown improved efficacy and long-term tolerability in patients who have radiographically progressed on or after treatment with one prior anti-PD-1 or anti-PD-L1 ICI and platinum-containing chemotherapy for metastatic disease. The combination of atezolizumab and cabozantinib has not been evaluated in squamous NSCLC. However, single-agent activity of atezolizumab (Rittmeyer et al. 2017; Section 1.2) and cabozantinib (Schöffski et al. 2017; Section 1.3) has been demonstrated in studies that evaluated both nonsquamous and squamous NSCLC where a similar treatment effect was observed with both histologies. Atezolizumab and cabozantinib have each demonstrated single-agent clinical activity in previously treated patients with NSCLC (Sections 1.2 and 1.3). The safety profile of each of the constituents of the combination is well-defined, and the combination has been studied in previous clinical trials with manageable safety profile. Dose management guidelines are included in the current study protocol for the most important risks.

Thus, the overall benefit–risk assessment is deemed favorable.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory

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

A possible consequence of inhibiting the PD-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 is 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 is associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. 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 treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

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

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab and cabozantinib 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, and pharmacokinetics of atezolizumab when given in combination with cabozantinib (Atezo + Cabo) compared with docetaxel monotherapy in patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* translocation, who have progressed on prior treatment with both anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- OS, defined as the time from randomization to death from any cause

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumor, Version 1.1. (RECIST v1.1), or death from any cause (whichever occurs first)
- Confirmed ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of response (DOR) for patients with confirmed ORR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)
- Time to confirmed deterioration in patient-reported Physical Function (PF) and global health status (GHS) as measured by the corresponding scores from the

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

- PFS rates assessed by the investigator at 6 months and at 1 year
- OS rates at 1 and 2 years

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Change from baseline and proportion of patients who report deterioration, improvement, or no change in their symptoms and functioning including quality of life (QoL) as measured by the EORTC Quality of Life–Lung Cancer 13-Item Questionnaire (EORTC QLQ-LC13) symptom scores (cough, dyspnea, chest pain, arm/shoulder pain, or fatigue) and EORTC QLQ-C30 functioning scores (PF, Role Function [RF], GHS)

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of Atezo + Cabo compared with docetaxel monotherapy on the basis of the following endpoint:

- Incidence and severity of adverse events with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

The exploratory safety objective for this study is to evaluate the safety of Atezo + Cabo compared with docetaxel monotherapy from the patient's perspective on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as determined through the use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) (see Appendix 12)
- Change from baseline in selected symptoms frequently reported with the intake of atezolizumab, cabozantinib, or docetaxel, as assessed through use of the PRO-CTCAE
- Frequency of patients' response of the degree they are troubled with treatment symptoms, as assessed through use of the single item EORTC Item List 46 (EORTC IL46)

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of Atezo + Cabo on the basis of the following endpoints:

- Serum concentration of atezolizumab at specified timepoints
- Plasma concentration of cabozantinib at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to Atezo + Cabo on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after treatment

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs to atezolizumab on the basis of the following endpoint:

- Relationship between atezolizumab ADA status and efficacy, safety, or PK endpoints

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to Atezo + Cabo (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to Atezo + Cabo, can provide evidence of Atezo + Cabo activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in peripheral blood mononuclear cells (PBMC), plasma, serum, and tumor tissue (including, but not limited to, PD-L1, PD-1, somatic mutations, and others) and efficacy, PK, immunogenicity, or other biomarker endpoints.

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with Atezo + Cabo compared with docetaxel monotherapy to inform pharmacoeconomic modeling on the basis of the following endpoints:

- Health utility scores from the EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-based at each timepoint
- Change from baseline at each timepoint using the EQ-5D-5L visual analog scale (VAS) scores

3. STUDY DESIGN

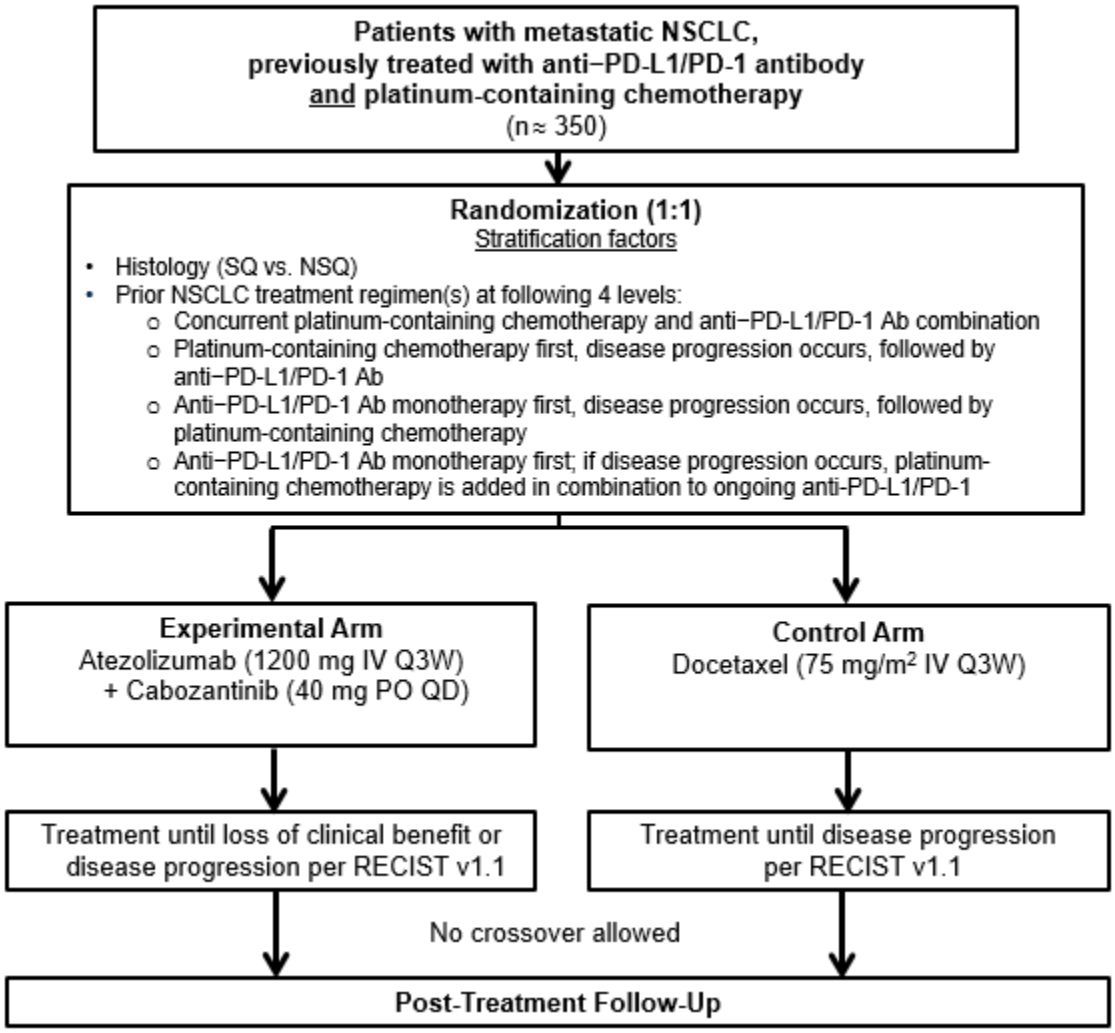
3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab given in combination with cabozantinib compared with docetaxel monotherapy in patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* translocation, who have progressed following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially.

Approximately 350 eligible patients will be randomized in a 1:1 ratio at approximately 125 global sites in this trial.

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

Figure 1 Study Schema



Ab = antibody; NSCLC = non–small cell lung cancer; NSQ = nonsquamous; PO = by mouth; QD = once a day; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SQ = squamous.

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities in Appendix 1. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1). Screening period may be extended per investigators discretion based on extenuating circumstances (i.e., delayed laboratory results).

Patients with tumors of nonsquamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested either locally using a validated health

authority–approved test or via central laboratory prior to enrollment (see specific exclusion Section 4.1.2). Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested (see specific exclusion criteria in Section 4.1.2).

Eligible patients will be in a randomized 1:1 ratio to receive either atezolizumab plus cabozantinib or docetaxel monotherapy. Randomization will be stratified by:

- Histology: nonsquamous versus squamous
- Prior NSCLC treatment regimen(s) at the following four levels:
    1. Concurrent platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody combination
    2. Platinum-containing chemotherapy first, disease progression occurs, followed by anti–PD-L1/PD-1 antibody
    3. Anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by platinum-containing chemotherapy without anti–PD-L1/PD-1 antibody
    4. Anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with platinum-containing chemotherapy added on

In the experimental arm, atezolizumab (fixed dose of 1200 mg) will be administered by IV infusion on Day 1 of each 21-day cycle. Cabozantinib (40 mg) will be administered orally in tablet form (two tablets of 20 mg each) QD on Days 1–21 of each cycle. In the control arm, docetaxel (75 mg/m^2) will be administered by IV on Day 1 of each 21-day cycle.

In the experimental arm: Atezolizumab and cabozantinib treatment will continue until unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). During study treatment, patients who meet criteria for disease progression per RECIST v1.1 and show evidence for clinical benefit may continue atezolizumab and/or cabozantinib treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression

- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom other treatment options and/or standard therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression

Patients randomized to the experimental arm may be allowed to discontinue one component of the combination study treatment but continue to receive the other component.

In the control arm: Docetaxel treatment will continue until unacceptable toxicity or disease progression as assessed by the investigator per RECIST v1.1.

Crossover from the control-arm to the experimental-arm will not be allowed.

Patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following Day 1 of Cycle 1, and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment regardless of treatment delays. Patients will continue scanning regardless of treatment delays until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above (i.e., every 6 weeks [±7 days] for the first 48 weeks and every 9 weeks [±7 days] after 48 weeks) until study treatment is discontinued.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

Response will be assessed according to RECIST v1.1 (see Appendix 3).

During the study, patients will be asked to complete patient-reported outcome (PRO) surveys at the beginning of the study (i.e., Day 1 of Cycle 1), on Day 1 of each cycle after Day 1 of Cycle 1, at treatment discontinuation, and during survival follow-up at 3 and 6 months (see Section 4.5.9 and Appendix 1). *Completion of PRO questionnaires will no longer be required after the final OS analysis.*

After study treatment discontinuation, survival follow-up information will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see Section 4.6.1). All patients will be periodically contacted for survival and new anti-cancer therapy information 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). *After completion of final OS analysis, patients will only need to be followed for 6 months after the last dose of study treatment and information on new anti-cancer therapy will no longer be required.* If the patient withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety data and will review the interim analysis for OS. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities and meeting frequencies.

Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months or as needed from the time of enrollment of the first patient. Unblinded efficacy data will be reviewed as part of an interim analysis for OS (see Section 6.10). All summaries and analyses for the iDMC review will be prepared by an external independent Data Coordinating Center.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. For the interim analysis of OS, the iDMC will review the analysis results provided by the iDCC and will recommend or not recommend to unblind the study to the Sponsor. Final decisions will rest with the Sponsor. Details will be specified in the iDMC charter.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

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

- The required number of deaths for the final analysis of OS has been observed (see Section 6.4.1) *or the last data point required for safety follow-up is received, whichever occurs later.*
- *The last patient's last visit has occurred.*

In addition, the Sponsor may decide to terminate the study at any *time and provide a written notification to investigators. Patients may continue study treatment until the development of progressive disease, unacceptable toxicity, patient consent withdrawal, or Sponsor's decision to terminate the study, whichever occurs first. If the Sponsor decides to end the study, patients still receiving study treatment may be offered participation in the continued access program or enrollment into another study for continued access to study treatment, if, in the opinion of the investigator and in consultation with the Medical Monitor, the patient would potentially benefit from continuing therapy and the patient cannot reasonably access the treatment outside of the program.*

The approximate total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 47 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic NSCLC after Progression on Prior Platinum-Containing Chemotherapy and Anti–PD-L1/PD-1 Antibody

As outlined in Section 1.3, in addition to multiple RTKs such as VEGFR2, MET, and RET, cabozantinib also inhibits TYRO3, AXL, and MER (TAM family kinases). The latter are implicated in promoting suppression of an antitumor immune response. Preclinical studies (Kwilas et al. 2014; Song et al. 2015; Lu et al. 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in patients with cancer (Apolo et al. 2014) suggest that cabozantinib promotes an immune-permissive environment, which might present an opportunity for synergistic effects from combination treatment with anti–PD-L1/PD-1 ICIs independent of PD-L1 expression.

Cabozantinib in combination with atezolizumab is currently being evaluated in a multi-cohort Phase Ib study in patients with locally advanced or metastatic solid tumors (COSMIC-021) (see the Cabozantinib Investigator's Brochure for more information). In Study COSMIC-021, encouraging clinical activity and tolerability of this combination was observed. Thus, this combination holds promise as a potential new treatment opportunity in patients with metastatic NSCLC who have limited treatment options after failure of anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy.

This randomized, open-label, Phase III study of the efficacy and safety of atezolizumab in combination with cabozantinib versus docetaxel monotherapy in patients with metastatic NSCLC who have progressed on prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody will test this hypothesis.

3.3.2 Rationale for Control Arm

For patients with metastatic NSCLC, after failure of initial systemic chemotherapy and anti–PD-L1/PD-1 treatment (either sequentially or concurrently), subsequent treatment options based on NCCN or ESMO guidelines include a) docetaxel; b) pemetrexed; and c) docetaxel and ramucirumab. Of these options, docetaxel is the most frequently used treatment option in this setting globally.

Docetaxel is approved in the United States as a single agent for locally advanced or metastatic NSCLC after platinum therapy failure and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (Taxotere® USPI) and also approved in the European Union for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy (Taxotere EMA SmPC).

More recently, the combination of docetaxel and ramucirumab was approved in the United States and the European Union for the second- and third-line treatment of metastatic NSCLC, based on the results of a large Phase III study comparing docetaxel and ramucirumab versus docetaxel monotherapy (n = 1253 patients). The study demonstrated a modest increase in median PFS (4.5 vs. 3.0 months) and median OS (10.5 vs. 9.1 months) (Garon et al. 2014). This modest improvement in efficacy was seen in both squamous and nonsquamous histologies.

Currently, docetaxel monotherapy continues to be widely used in this patient population. Several recent randomized Phase III trials in NSCLC in second- and third-line treatment of patients with metastatic NSCLC have been designed with docetaxel as the active control arm (Borghaei et al. 2015; Herbst et al. 2016; Rittmeyer et al. 2017). Thus, based on the global treatment landscape, docetaxel will be used as the comparator in this study.

3.3.3 Rationale for Study Treatment Dose Selection and Treatment Schedule

3.3.3.1 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 an approved dose regimen for atezolizumab (Tecentriq USPI) in NSCLC, and this atezolizumab dose regimen is also currently being evaluated in the Phase Ib study (COSMIC-021) of atezolizumab and cabozantinib. 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 DLTs 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).

3.3.3.2 Rationale for Cabozantinib Dose and Schedule

In this Phase III study, the starting cabozantinib dose will be 40 mg QD based on results from the ongoing Phase Ib study (COSMIC-021) evaluating atezolizumab in combination with cabozantinib (Section 1.4). In the Phase Ib study, a total of 12 patients with advanced RCC were evaluated in the dose-escalation stage at the 40-mg or 60-mg cabozantinib dose level (6 patients each) plus the standard dose of atezolizumab. After reviewing all available safety and efficacy data of the dose-escalation stage, the Cohort Review Committee determined that cabozantinib 40 mg QD orally in combination with 1200 mg atezolizumab Q3W IV is the recommended dose for the expansion-stage combination-therapy cohorts. The Cohort Review Committee decision was based on the favorable safety profile of the 40-mg cabozantinib dose level over a prolonged time on study treatment with less frequent dose reductions and encouraging preliminary efficacy, which was deemed to optimize the benefit–risk of the combination therapy in multiple solid tumor expansion cohorts including an NSCLC cohort.

The lower 40-mg dose of cabozantinib in combination with atezolizumab is further supported by an exposure-response analysis of safety and efficacy endpoints from cabozantinib monotherapy data in the METEOR trial in 2L RCC evaluating 60-mg cabozantinib versus everolimus (Lacy et al. 2018). Dose reductions to 40 mg and then 20 mg were allowed and occurred in 62% of patients in the cabozantinib group. The 60-mg exposure was associated with a higher risk for selected adverse events including PPE (Grade ≥ 1), fatigue/asthenia (Grade ≥ 3), hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), and diarrhea (Grade ≥ 3), with predicted HRs of 1.49, 1.42, 1.36, and 1.33, respectively, relative to the predicted average steady-state cabozantinib concentration for a 40-mg starting dose. While the efficacy was somewhat lower with a 40-mg monotherapy dose compared to the 60-mg dose (higher risk of disease progression/death (HR $= 1.1$), lower maximal median reduction in tumor size (-9.1% vs. -11.9%) and lower ORR (15.6% vs. 19.1%), the benefit–risk in combination with atezolizumab based on the dose-escalation stage of the COSMIC-021 Phase Ib study favored the lower 40-mg cabozantinib dose, considering the potential overlapping adverse events of the two agents.

3.3.4 Rationale for Patient Population and Analysis Groups

There is a significant unmet need in patients with metastatic NSCLC who have progressed following prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody either in combination or in sequence. Currently, single-agent chemotherapy is the main treatment option available to these patients but has modest activity as described above. Both atezolizumab and cabozantinib have shown single-agent activity in multiple tumor types, including NSCLC. Moreover, atezolizumab is approved as monotherapy for patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy (Tecentriq USPI), or as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (Tecentriq SmPC). The encouraging observed clinical activity and

tolerability of this combination hold promise as a potential new treatment opportunity in patients with metastatic NSCLC who have progressed on prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody. This randomized, open-label, Phase III study of the efficacy and safety of atezolizumab in combination with cabozantinib versus docetaxel monotherapy in patients with metastatic NSCLC who have progressed on prior platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody will test this hypothesis. Patients whose tumors have *EGFR* mutations or *ALK* translocation for which targeted therapy is approved are excluded irrespective of whether such therapy has previously been given.

3.3.5 Rationale for Open-Label Study

An open-label study design was chosen for this trial, and this allows for adequate side effect management given the different toxicity profiles associated with each study drug. Furthermore, a blinded study would require administration of IV placebo, which could pose additional burden to patients. Finally, because of the potential for pseudoprogression in patients randomized to the experimental arm, a blinded study would require all patients to continue treatment until loss of clinical benefit regardless of the arm to which they are randomized. This could then delay subsequent treatment with approved therapies, as well as increase the complexity of treatment decisions for patients on the docetaxel arm.

3.3.6 Rationale for Treatment beyond Initial Radiographic Progression per RECIST v1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (PD) (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow patients randomized to receive atezolizumab plus cabozantinib to continue to receive study treatment after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable (see criteria in Section 3.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

3.3.7 Rationale for Biomarker Assessments

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). In the current study, any tumor samples collected will be tested for PD-L1 expression by a central laboratory. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit and safety of atezolizumab and cabozantinib, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed. DNA

and/or RNA extraction and analysis may be performed to enable next-generation sequencing (NGS), including but not limited to whole exome sequencing (WES), to evaluate expression of genes to assess their association with efficacy, and to identify somatic mutations to increase understanding of disease pathobiology. Methods for the biomarker analysis may also include, but are not limited to, digital polymerase chain reaction (PCR), quantitative reverse transcription–PCR, and proteomics-based approaches.

Fresh tumor biopsy, when clinically feasible, is preferred. Tumor tissue will also be collected at the time of first evidence of radiographic disease progression per RECIST v1.1, if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab.

Blood-based biomarkers (including, but not limited to, circulating tumor DNA [ctDNA]) may be also evaluated and correlated with Atezo + Cabo efficacy and evaluated as surrogate markers of efficacy. This evaluation of blood-based markers may provide evidence for biologic activity of Atezo + Cabo in patients with NSCLC, help to identify patients who may benefit most from Atezo + Cabo, and help future development of tissue-free diagnostic options for patients who have inadequate quality or insufficient quantity of tumor tissue for biomarker testing.

Blood samples will be collected in order to better understand the changes in blood-based biomarker profiles and potential mechanisms of resistance upon progression. Blood samples may also be evaluated for additional exploratory biomarkers that may be associated with the therapeutic effects of Atezo + Cabo or the pathogenesis of NSCLC.

Tissue samples will be collected for DNA extraction to enable WES to identify variants that are predictive of response to study drugs, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. WES provides a comprehensive characterization of the exome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

3.3.8 Rationale for Patient-Reported Assessments

In the treatment of lung cancer, it is important to both increase survival and minimize symptoms by delaying progression because symptoms have negative impacts on patients' functioning including health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). Patients are uniquely qualified to report their symptom severity and how it impacts their daily functioning and overall QoL. Therefore, PROs will complement traditional evaluation of survival and tumor progression (see Section 2.1.2). In addition, many of the most frequent adverse events attributed to atezolizumab, cabozantinib, or docetaxel (e.g., fatigue, rash, nausea) are symptoms directly reportable by patients; therefore, patients' reporting of their experience with these symptoms will complement the evaluation of treatment tolerability (King-Kallimanis et al. 2019).

This study includes use of validated patient-reported measures of symptom severity and symptom impact on functioning including HRQoL: the EORTC QLQ-C30; its lung-specific module EORTC QLQ-LC13; and selected scales from the PRO-CTCAE item library to reflect known experience receiving atezolizumab, cabozantinib, and docetaxel, including one-item EORTC IL46 to document overall treatment burden. Data generated from these questionnaires will inform patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the risk–benefit of atezolizumab and cabozantinib.

Although the patients will not be blinded to their treatment, to date, upon examination of open-label studies, there is no empirical evidence that assessor bias is of such magnitude as to alter the findings particularly when ratings are on specific concepts as symptoms severity and symptoms interference with daily functioning (Atkinson et al. 2017; Roydhouse et al. 2019).

The EQ-5D-5L is also included in this study to generate utility scores for use in economic models for reimbursement.

3.3.9 Rationale for Stratification Factors

To balance key clinical risk factors between the two treatment arms, randomization will be stratified as follows:

- Histology: squamous vs. nonsquamous
- Prior NSCLC treatment regimen(s) at the following four levels:
    1. Patients who have received concurrent platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody combination
    2. Patients who have received platinum-containing chemotherapy first, disease progression occurs, followed by anti–PD-L1/PD-1 antibody

3. Patients who have received anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by platinum-containing chemotherapy without anti-PD-L1/PD-1 antibody
4. Patients who have received anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with platinum-containing chemotherapy added on

The rationale for including each of these stratification factors is described below.

Histology

Since anti–PD-L1/PD-1 antibodies appear to be equally efficacious in both squamous and nonsquamous histologies, this study will allow patients with either squamous or nonsquamous NSCLC to be enrolled. However, it is well documented that median OS is shorter in patients with metastatic NSCLC with squamous histology than nonsquamous histology. Therefore, histology is selected as a stratification factor to minimize any imbalance in these subgroups.

Prior NSCLC Treatment Regimens

A number of factors relating to prior NSCLC regimen may be associated with differing clinical outcomes, including the number, order of prior lines of therapy, and last type of therapy type received.

For example, patients who have progressed on platinum-containing chemotherapy followed by anti–PD-L1/PD-1 antibody (two prior lines of therapy) may have poorer outcomes than patients who have progressed on prior anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy in combination (i.e., one prior line of therapy) on the basis of having failed more lines of treatment. For example, in the 2L/3L NSCLC OAK study (Rittmeyer et al. 2017), 2L patients had better OS outcome than 3L patients (OS HR of 0.71 in 2L vs. 0.80 in 3L, in favor of atezolizumab).

In addition to the number of prior regimens, proximity to last anti–PD-L1/PD-1 antibody treatment may correlate with outcomes as any intervening therapy may impact observed efficacy associated with re-challenge.

Given the uncertainty regarding the underlying biology including mechanisms of resistance for anti–PD-L1/PD-1 antibody refractory versus anti–PD-L1/PD-1 antibody resistant NSCLC, sequencing of therapy, and last type of therapy; a multi-factor stratification factor will be used to maintain balance between study arms.

Stratification on all permutations of when and in what combination prior anti–PD-L1/PD-1 antibody was received will minimize potential imbalances that may impact efficacy with re-challenge with an anti–PD-L1/PD-1 antibody.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 350 patients with metastatic NSCLC will be enrolled during the global enrollment phase of this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for entry into the study:

- Signed informed consent form
- Age ≥ 18 years old or meeting country definition of adult, whichever is older, on the day of consent
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed metastatic NSCLC
- Documented radiographic disease progression during or following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially for metastatic NSCLC

  If anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy are given concurrently as the first-line treatment for metastatic NSCLC, no further lines of systemic anti-cancer therapy are allowed.

  If anti–PD-L1/PD-1 antibody and platinum-containing chemotherapy are given sequentially as first and second lines, respectively, for metastatic NSCLC, no further lines of systemic anti-cancer therapy are allowed.

  Combination therapies with other agents are allowed with anti–PD-L1/PD-1 and/or platinum-containing chemotherapy (see exclusion criteria for exceptions).
- Measurable disease per RECIST v1.1 outside CNS as assessed by investigator

  Previously irradiated lesions can be considered as measurable disease only if PD has been unequivocally documented at that site since radiation.
- Known PD-L1 status or availability of tumor tissue for central PD-L1 testing:
  - Availability of representative fresh and archival tumor specimens suitable for determination of PD-L1 status via central testing (see Section 4.5.7 for tissue requirements). Results of central PD-L1 testing are not required for patient to be randomized into the study.

    If obtaining representative fresh tumor is not clinically feasible, representative archival tumor specimen is acceptable.
  - If no tissue specimen (fresh or archival) is available, documentation of known PD-L1 status as established by a health authority–approved PD-L1 assay is required.
- ECOG Performance Status score of 0 or 1

- Recovery to baseline or Grade ≤ 1 NCI CTCAE v5.0 from toxicities related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable on supportive therapy in the opinion of the investigator

  Grade 2 alopecia is allowed for study participation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - ANC $\geq$ 1500/µL ($\geq 1.5 \times 10^9$/L) without granulocyte colony-stimulating factor support within 14 days of laboratory sample collection
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/µL)
  - Platelets ≥ 100,000/µL ($\geq 100 \times 10^9$/L) without transfusion within 14 days of laboratory sample collection
  - Hemoglobin $\geq$ 9 g/dL ($\geq$ 90 g/L) without transfusion within 14 days of laboratory sample collection
  - Serum bilirubin $\leq 1.0 \times$ upper limit of normal (ULN)
  - Liver function tests meeting one of the following criteria:

    ALT and AST $\leq 2.5 \times$ ULN with ALP $\leq 2.5 \times$ ULN,

    OR

    ALT and AST $\leq 1.5 \times$ ULN with ALP $> 2.5 \times$ ULN
  - Serum creatinine $\leq$ 1.5 $\times$ ULN or calculated creatinine clearance $\geq$ 40 mL/min (using the Cockcroft-Gault equation):

    For males: (140 – age) $\times$ weight (kg)/(serum creatinine [mg/dL] $\times$ 72)

    For females: Multiply above value by 0.85.
  - Albumin $\geq$ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
  - Urine protein/creatinine ratio $\leq$ 1 mg/mg ($\leq$ 113.2 mg/mmol) or 24-hour urine protein < 1 g
- 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 negative HBsAg test and 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 contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use two methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The recommended highly effective methods of contraception are defined in Appendix 8.

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

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

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 4 months after the final dose of cabozantinib, or for 6 months after the final dose of docetaxel. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment with atezolizumab in combination with cabozantinib in the

experimental arm or during the treatment with docetaxel in the control arm, and for 4 months after the final dose of cabozantinib to avoid exposing the embryo.

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

4.1.2 Exclusion Criteria

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

- Prior therapy with the following agents for NSCLC:
  - Cabozantinib
  - Docetaxel
  - Combination of an anti–PD-L1/PD-1 antibody concurrently with a VEGFR-targeting TKI
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Documentation of known sensitizing mutation in the *EGFR* gene or *ALK* fusion oncogene
  - Patients with nonsquamous NSCLC who have an unknown *EGFR* or *ALK* status will be required to be tested at screening.
  - Patients with squamous NSCLC who have an unknown *EGFR* or *ALK* status are eligible and will not be required to be tested at screening.
  - *EGFR* and/or *ALK* status may be assessed locally or at a central laboratory.

    EGFR status assessed locally must be performed on tissue or cytology using a validated health authority–approved test that detects mutations in exons 18–21.

    If samples are submitted for central *EGFR* and/or *ALK* testing, additional slides must be provided (see Section 4.5.7 for details).
- Patients with known *ROS1* rearrangements, *BRAF* V600E mutations, or other actionable oncogenes with approved therapies if available

- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1 as assessed by investigator, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.

– If the patient is receiving anticonvulsant therapy, the dose is considered stable.

- History of leptomeningeal disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (more frequently than once monthly)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Severe hepatic impairment (Child-Pugh B or C)
- Uncontrolled or symptomatic hypercalcemia
- Any other active malignancy at the time of initiation of study treatment or diagnosis of another malignancy within 3 years prior to initiation of study treatment that

requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, incidental prostate cancer, or carcinoma in situ of the prostate, cervix, or breast

- Stroke, transient ischemic attack (TIA), myocardial infarction or other symptomatic ischemic events within 6 months of initiation of study treatment
- Significant vascular disease (e.g., aortic aneurysm or arterial dissection requiring surgical repair or recent peripheral arterial thrombosis) within 6 months of initiation of study treatment
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, unstable arrhythmia, or unstable angina) within 3 months prior to initiation of study treatment
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- 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 [COPD] exacerbation) are eligible for the study.
- Current treatment with anti-viral therapy for HBV
- Major surgical procedure, other than for diagnosis (e.g., gastrointestinal [GI] surgery, removal or biopsy of brain metastasis), within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Minor surgeries are not allowed within 10 days prior to initiation of study treatment. Patients must have complete wound healing from major surgery or minor surgery before initiation of study treatment. Patients with clinically relevant ongoing complications from prior surgery are not eligible.
- Pregnant or lactating females, or intention of becoming pregnant during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, or within 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later.

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Ongoing Grade $\geq$ 2 sensory or motor neuropathy
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid

antibody syndrome, granulomatosis $with\ polyangiitis$, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

Patients with controlled Type 1 diabetes mellitus 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.

- Pharmacologically uncompensated, symptomatic hypothyroidism
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Prior allogeneic stem cell or solid organ transplantation
- Administration of 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 final dose of atezolizumab
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–α[TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  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), inhaled or low-dose systemic corticosteroids for COPD or asthma, or low-dose

corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the cabozantinib formulation
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel)

  The following are anti-coagulants allowed in this study:

  In addition to prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose (prophylactic) low–molecular-weight heparins (LMWH), prophylactic dose of direct factor Xa inhibitors, rivaroxaban, edoxaban, or apixaban are permitted.

  Therapeutic doses of LMWHs or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed in patients without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor
- Thromboembolic event (e.g., deep vein thrombosis [DVT], pulmonary embolism) within 6 months before initiation of study treatment

  Patients with a diagnosis of DVT within 6 months are allowed if stable and treated with LMWH or direct factor Xa inhibitors, rivaroxaban, edoxaban, or apixaban for at least 1 week before initiation of study treatment.
- History of risk factors for torsades de pointes (e.g., long QT syndrome)
- Corrected QT interval corrected through use of Fridericia's formula (QTcF) >480 ms per ECG within 14 days before initiation of study treatment

  If a single ECG shows a QTcF with an absolute value >480 ms, two additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of the three consecutive results for QTcF must be ≤ 480 ms for the patient to be eligible.
- Uncontrolled hypertension defined as systolic blood pressure >150 mm Hg or diastolic BP >90 mm Hg despite optimal antihypertensive treatment

- Tumors invading the GI-tract, active peptic ulcer disease, acute pancreatitis, acute obstruction of the pancreatic or biliary duct, appendicitis, cholangitis, cholecystitis, diverticulitis, gastric outlet obstruction, or inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- Abdominal fistula, bowel obstruction, GI perforation, or intra-abdominal abscess within 6 months before initiation of study treatment

  Complete healing of an intra-abdominal abscess must be confirmed before initiation of study treatment.
- Known cavitating pulmonary lesion(s) or known endobronchial disease manifestation
- Lesions invading major pulmonary blood vessels
- Clinically significant hematuria, hematemesis, hemoptysis of $>$0.5 teaspoon (2.5 mL) of red blood, coagulopathy, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before initiation of study treatment
- Serious non-healing wound/ulcer/bone fracture
- Malabsorption syndrome
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption are also excluded.
- Requirement for hemodialysis or peritoneal dialysis
- Inability to swallow tablets

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

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

Patients will be randomly assigned to one of two treatment arms: Experimental arm (atezolizumab 1200 mg IV Q3W + cabozantinib 40 mg PO QD) or control arm (docetaxel 75 mg/m² IV Q3W). Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following factors:

- Histology (nonsquamous vs. squamous)
- Prior NSCLC treatment regimen(s) at the following four levels:
  1. Concurrent platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody combination

2. Platinum-containing chemotherapy first, disease progression occurs, followed by anti–PD-L1/PD-1 antibody
3. Anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by platinum-containing chemotherapy without anti-PD-L1/PD-1 antibody
4. Anti–PD-L1/PD-1 antibody monotherapy first, disease progression occurs, followed by continued anti-PD-L1/PD-1 antibody in combination with platinum-containing chemotherapy added on

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 3 days after randomization.

4.2.2 Blinding

Although this is an open label study, the study team at the Sponsor consisting of clinical, statistical, statistical programming, data management, and other study personnel, will be blinded to the randomized treatment assignment by IxRS.

The study team will not be allowed to perform analyses or summaries generated by randomized treatment assignment and/or actual treatment received before the randomized treatment assignment for all randomized patients is disclosed to the study team for the prespecified analysis.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab, cabozantinib, and docetaxel.

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 Cabozantinib

Cabozantinib will be supplied by the Sponsor as 20-mg yellow film-coated round tablets. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 1.

Table 1 Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib drug substance (25% drug load as free base)	Active ingredient	31.68
Microcrystalline cellulose (Avicel® PH-102)	Filler	38.85
Lactose anhydrous (60M)	Filler	19.42
Hydroxypropyl cellulose (EXF)	Binder	3.00
Croscarmellose sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal silicon dioxide	Glidant	0.30
Magnesium stearate	Lubricant	0.75
Opadry® yellow film coating, which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film coating	4.00

HPMC = hydroxypropyl methylcellulose.

[a] Weight fraction, expressed in percentage.

For information on the formulation and handling of cabozantinib, see the pharmacy manual and/or the Cabozantinib Investigator's Brochure.

4.3.1.3 Docetaxel

Docetaxel will be used in commercially available formulation, packaging, and handling. Docetaxel will be provided by the Sponsor where it is considered an IMP by local regulations (see Section 4.3.3).

For information on the formulation, packaging, and handling of docetaxel, see the local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Sections 4.3.2.1 and 4.3.2.2.

Patients in the experimental treatment arm will receive atezolizumab 1200 mg IV on Day 1 of each 21-day cycle and 40 mg of cabozantinib (two tablets of 20 mg each) orally QD on Days 1–21 of each cycle.

Patients in the control arm will receive docetaxel 75 mg/m² IV Q3W.

Administration of atezolizumab and docetaxel 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. In addition, the first dose of cabozantinib is to be administered at the clinic. For anaphylaxis precautions, see Appendix 5.

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

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

4.3.2.1 Experimental Arm

Atezolizumab will be administered first on days when both atezolizumab and cabozantinib are to be given.

Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. For Cycle 1, premedication administered for atezolizumab is not permitted. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 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 and after the infusion of atezolizumab, but prior to the administration of cabozantinib. • 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 every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 6.

Cabozantinib

Cabozantinib will be administered orally, QD at a dose of 40 mg (2 × 20-mg tablets) on Days 1–21 of each cycle.

First Dose of Cabozantinib

Cabozantinib will be administered after completion of atezolizumab infusion. Patients will fast (with the exception of water) for at least 2 hours before receiving cabozantinib. Upon completion of the 2-hour fast, the patient will receive the oral dose of cabozantinib with a minimum of 8 oz (240 mL) of water in the clinic and then continue to fast for an additional 1 hour.

If the patient develops an infusion reaction during or after atezolizumab infusion, the administration of oral cabozantinib will be delayed or interrupted until the patient has recovered and the investigator believes that it is safe to administer cabozantinib.

Subsequent Doses of Cabozantinib

Patients should take cabozantinib outside the clinic at approximately the same time every day, preferentially before going to bed.

Patients will fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose. After the 2-hour fast and before going to bed, patients are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no food intake for one more hours postdose. If the patient's schedule requires taking cabozantinib during the day, the patient is to be instructed to follow the same fasting recommendations.

Tablets should not be crushed or chewed. Grapefruit and Seville oranges (and products made from them) should be avoided while being treated with cabozantinib.

Patients are to be instructed to not make up vomited doses of oral study treatment and to maintain the planned dosing schedule. Patients are not to make up for missed doses if more than 12 hours have elapsed after the time the patient would usually take cabozantinib. In the event of missed doses, patients are not to take two doses to make up for the one the patient missed.

Any unused oral study treatment must be returned to the study site for drug accountability and disposal.

Guidelines for dosage modification, treatment interruption or discontinuation for patients who experience adverse events with cabozantinib are provided in Appendix 7.

4.3.2.2 Control Arm

Docetaxel will be administered by IV infusion at a starting dose of 75 mg/m^2 Q3W according to the locally approved label.

All patients randomized to receive docetaxel should be pre-medicated with corticosteroids according to local practice (e.g., oral dexamethasone at 16 mg per day [administered as 8 mg twice daily], for 3 days starting a day prior to docetaxel administration) to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions. Anti-emetic prophylaxis may be administered at the treating physician's discretion according to local practice.

Vital signs will be collected for docetaxel infusions according to Section 4.5.4.

Guidelines for dosage modification, treatment interruption or discontinuation for patients who experience adverse events with docetaxel are provided in Section 5.

4.3.3 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, cabozantinib, and docetaxel. All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Atezolizumab and Cabozantinib

The Sponsor will offer continued access to study treatment (atezolizumab and cabozantinib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive atezolizumab and/or cabozantinib after completing the study if all of the following conditions are met:

- The patients' underlying disease is life-threatening and requires continued study treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive atezolizumab and/or cabozantinib after completing the study if any of the following conditions are met:

- The study treatment is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for NSCLC.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for NSCLC.
- Provision of the study treatment is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone replacement

- Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines)
- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:

  Low dose LMWH for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. Note: Anticoagulation with the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor betrixaban is not allowed.

  Therapeutic doses of LMWH or anticoagulation with direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban after first dose of study treatment are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. Note: Anticoagulation with the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor betrixaban is not allowed. For management of thromboembolic complications while on study, refer to Appendix 7.

  Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and nonsteroidal anti-inflammatory drugs should not be used concomitantly with heparin or factor Xa inhibitors due to the increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines.

- Vaccinations (such as influenza, SARS-CoV-2)
  - Live, attenuated vaccines are not permitted (see Section 4.4.7)

- 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
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

    Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab, cabozantinib, and docetaxel may be continued during palliative radiotherapy.

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 – 4.4.7) 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 5).

4.4.2 Cautionary Therapy for All Patients

4.4.2.1 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 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.3.1 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 Appendix 6 for details).

4.4.4 Cautionary Therapy for Cabozantinib Treated Patients

4.4.4.1 Cytochrome P450

Data from a clinical drug interaction study (XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration–time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and, by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (i.e., CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce CYP enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (i.e., AUC) to cabozantinib. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a patient who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase

cabozantinib concentrations. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (i.e., AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the drug interaction tables at the following website for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions.

4.4.4.2 Protein Binding

Cabozantinib is highly bound (≥99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

4.4.4.3 Other Interactions

Food may increase exposure levels of cabozantinib by 57%; fasting recommendations (see Section 4.3.2.1) should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Patients should be cautioned against taking a P-glycoprotein substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). In addition, cabozantinib was shown to be a substrate of drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay. Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g., cyclosporine, efavirenz, emtricitabine) should be approached with caution. Additional details related to these overall conclusions can be found in the investigator brochure.

Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure and should be avoided.

Administration of the proton-pump inhibitor esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., proton-pump inhibitors, H_2 receptor antagonists, and antacids) is not contraindicated in patients administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the Cabozantinib Investigator's Brochure.

4.4.5 Cautionary Therapy for Docetaxel-Treated Patients

Docetaxel is a CYP3A4 substrate. Patients randomized to receive docetaxel must avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors.

In addition, concomitant treatment with CYP3A4 inducers may decrease plasma concentrations of docetaxel. Therefore, concomitant medications that are CYP3A4 inducers should be used with caution.

Granulocyte colony-stimulating factor treatment is permitted for patients in the docetaxel arm. The primary prophylaxis should be administered per the American Society of Clinical Oncology, EORTC, and ESMO guidelines; namely, in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

Anti-emetics, anti-allergic measures, and other treatments for concomitant docetaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

See the Summary of Product Characteristics for docetaxel for all boxed warnings and contraindications.

4.4.6 Prohibited Therapies for All Patients

Use of the following concomitant therapies is prohibited for all patients:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment, until disease progression is documented and the patient has discontinued study treatment (see Section 4.6.2, with the exception of palliative radiotherapy).
- Any investigational therapy or investigational medical device is prohibited within 4 weeks prior to initiation of study treatment and during study treatment.

4.4.7 Prohibited Therapies for Atezolizumab-Treated and Cabozantinib-Treated Patients

Use of the following concomitant therapies is prohibited for patients treated with atezolizumab and cabozantinib:

- Live, attenuated vaccines (e.g., FluMist®, intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final 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.
- Oral anti-coagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitor dabigatran, direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low-dose levels for cardioprotection per local applicable guidelines), until 4 weeks after cabozantinib has been permanently discontinued (for permitted anti-coagulants, refer to Section 4.4.1.
- Concomitant medications known to prolong the QTc interval should be avoided in patients who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

4.4.8 Prohibited Food for Cabozantinib-Treated Patients

Use of the following foods is prohibited as described below:

- Consumption of grapefruit or grapefruit juice and potent CYP3A4 enzyme inhibitors is prohibited during the treatment with cabozantinib.

4.5 STUDY ASSESSMENTS

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

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

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN

services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional, but will not include study drug infusions, which must be performed at the study site. The schedules of activities (see Appendix 1 and Appendix 2) will specify the assessments that may be performed by an MN professional for patients in either arm. Investigators should ensure adequate clinical oversight.

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.

Evaluations (e.g., tumor imaging) performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Certain laboratory values must be obtained closer to randomization, within 14 days. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and use of alcohol and drugs of abuse, will be recorded at baseline. Prior PD-L1 testing and results will also be recorded in the eCRF. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the skin, head, eyes, ears, nose, and throat, the

cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, blood and lymphatic, 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 predose at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Refer to Appendix 1 for the schedule of physical examination and performance status assessments.

4.5.4 Vital Signs

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

For the first infusion, vital signs should be measured within 60 minutes prior to each atezolizumab and docetaxel infusion, after the infusion of atezolizumab but prior to the administration of cabozantinib, and, if clinically indicated, during or after the infusion as indicated in the schedule of activities (Appendix 1). If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. 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 and Response Evaluations

Screening assessments and subsequent tumor assessments must include CT scans (with oral or IV contrast) of chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed, and magnetic resonance imaging (MRI) scans of the abdomen and pelvis should be performed.

A CT scan with contrast or MRI scan of the head must also be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated at screening.

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

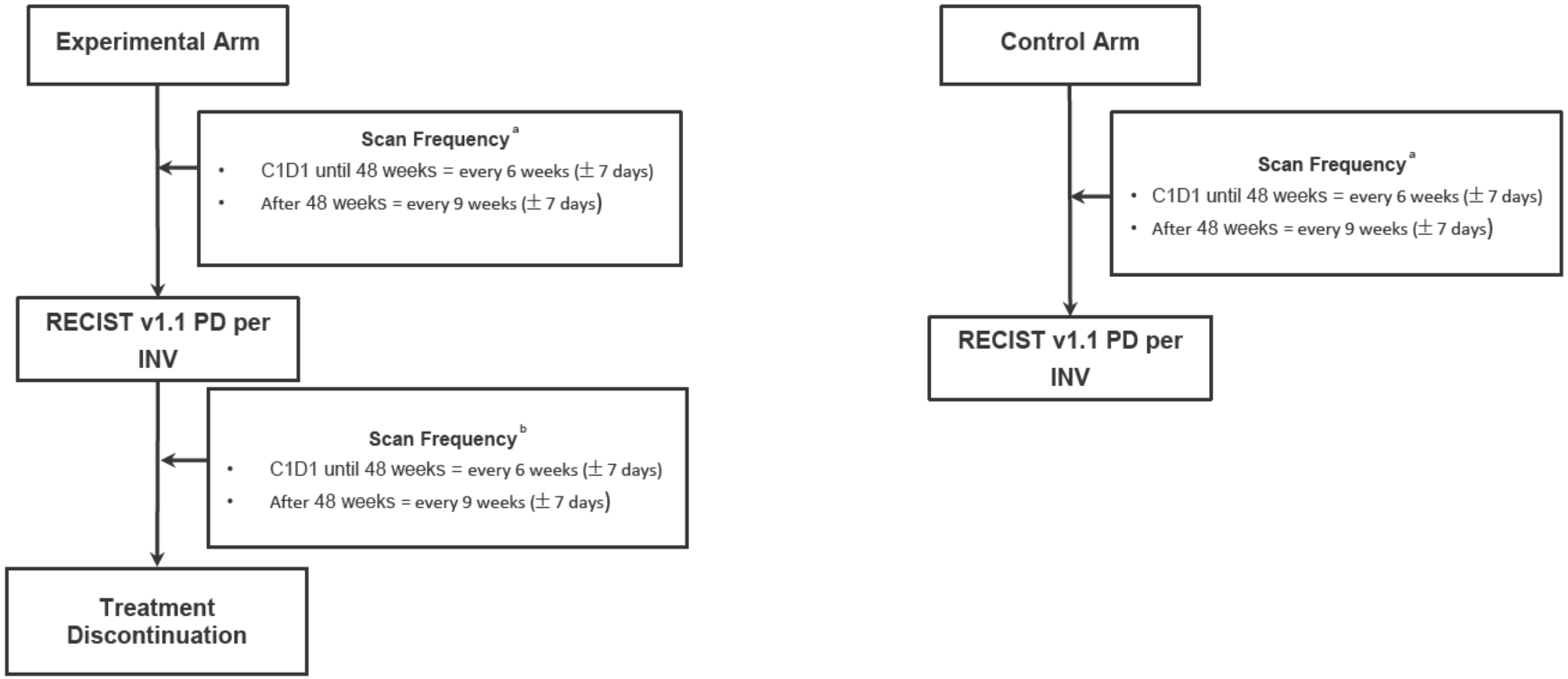
Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Day 1 of Cycle 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. At subsequent (post-screening) tumor assessments, patients with a history of irradiated brain metastasis at screening are not required to undergo brain scan unless clinically indicated. The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used to assess disease sites at screening should be used for subsequent tumor assessments.

Patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following Day 1 of Cycle 1, and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment regardless of treatment delays. Patients will continue scanning regardless of treatment delays until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans may be performed at any time if PD or loss of clinical benefit is suspected.

Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will continue to undergo tumor assessments at the frequency described above (i.e., every 6 weeks (±7 days) for the first 48 weeks and every 9 weeks (±7 days) after 48 weeks) until study treatment is discontinued.

See Figure 2 for representation of on-study scan frequency

Figure 2 Scan Frequency



C1D1 = Cycle 1, Day 1; INV = investigator; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumor, Version 1.1

[a] Patients who have discontinued treatment at the time of disease progression, as assessed by the investigator per RECIST v1.1, are not required to have further scans as part of the study.

[b] Patients treated beyond disease progression, as assessed by the investigator per RECIST v1.1, will continue to get scans per protocol at a frequency of every 6 weeks (± 7 days) for first 48 weeks and every 9 weeks (± 7 days) after 48 weeks until treatment discontinuation.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

A RECIST v1.1 PD-tumor assessment must be performed in both study arms and tumor assessments must be continued until treatment discontinuation for patients who receive treatment beyond progression in the experimental arm. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions at all subsequent assessments.

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.6 Survival Assessments

OS follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months (every 12 weeks [±7 days]) or more frequently until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from the survival follow-up (this request must be documented in the source documents and signed by the investigator). *After completion of final OS analysis, patients will only need to be followed for 6 months after the last dose of study treatment and information on new anti-cancer therapy information will no longer be required.* If the patient specifically withdraws from survival follow-up, the study staff may use a public information source (e.g., county records), per local regulations, to obtain information about survival status only.

See Appendix 1 for the schedule of follow-up assessments.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells [if applicable])
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium,

chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH

- Coagulation: INR and 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 free 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. HBV DNA test must be negative.
- 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
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will 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 postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Urine Chemistry (Protein [spot urine or 24-hour collection; fully quantitative]; Creatinine [spot urine; fully quantitative]; Urine protein/creatinine ratio [spot urine])
- 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 sample for analysis of C-reactive protein
- Serum samples for atezolizumab PK analysis through use of a validated assay
- Plasma samples for cabozantinib PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of a validated assay

- Blood, plasma, and serum samples for exploratory biomarker research, including biomarker assay development

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

- Representative fresh and archival tumor tissue sample obtained at baseline for exploratory research on biomarkers (e.g., PD-L1 status via central testing), including biomarker assay development. Tumor tissue samples should be submitted before or within 4 weeks of randomization.

  If obtaining representative fresh tumor is not clinically feasible, representative archival tumor specimen is acceptable.

  Representative formalin-fixed, paraffin-embedded tumor specimens in a paraffin block (preferred) or slides (preferably 15 or more) containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report. If 15 slides are not available, fewer can be submitted. A minimum of 5 slides is required for central PD-L1 testing.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples should be collected via resection, core-needle biopsy (at least 3, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

- For patients with nonsquamous NSCLC, if *EGFR* and/or *ALK* status is unknown, these must be assessed locally using a validated health authority–approved test or at a central laboratory (see Section 4.1.2 for exclusion criteria). If samples are submitted for central testing, an additional 5 unstained slides must be provided (see additional details in the laboratory manual).

- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible, for exploratory research on biomarkers, including biomarker assay development

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research in tumor tissue and blood may include, but will not be limited to, analysis of proteins, 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, ctDNA, or RNA, analysis of somatic mutations, and use of NGS (including but not limited to WES).

On the basis of emerging safety, activity, or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, these collected samples may not be analyzed if not warranted. After final OS analysis is conducted, the Sponsor may decide to no longer collect additional biomarker samples. The existing collected samples may still be used for exploratory analysis.

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 no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum and plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed, or earlier depending on local regulations.
- Blood and tumor samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final CSR has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- 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, including data on genomic variants, 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.

4.5.8 Electrocardiograms

At screening and during the study, single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine the corrected QT interval calculated using the Fridericia formula (QTcF). If at any time a single ECG shows a QTcF with an absolute value >480 ms or an increase in the QTcF of >60 ms above baseline, two additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of these three consecutive results for QTcF will be used as the value assessed (see Appendix 7).

ECGs will be performed at the timepoints as indicated in the schedule of activities (Appendix 1). 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.

Abnormalities in the ECG that lead to a change in patient management (e.g., dose reduced or interrupted, treatment discontinued, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be deemed adverse events. If values meet criteria defining them as serious, they must be reported as serious adverse events (Section 5.4.2).

The Fridericia formula is depicted below for calculation of the QTcF value.

QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate)

4.5.9 Patient-Reported Outcome Assessments

PRO questionnaires will be completed to more fully characterize the clinical profile of atezolizumab and cabozantinib to complement traditional endpoints of survival, tumor progression and tolerability. In addition, PRO questionnaires will enable the capture of each patient's direct experience with atezolizumab and cabozantinib.

PROs of symptom severity and functioning, including HRQoL, will be collected through use of the EORTC library, including the generic QoL questionnaires for cancer (EORTC

QLQ-C30), selected scales from the EORTC QLQ-C30 (EORTC IL17), its lung-specific module (EORTC QLQ-LC13), one item (IL46) documenting overall treatment burden, and selected items from the PRO-CTCAE library to inform symptoms commonly experienced while receiving atezolizumab, cabozantinib, or docetaxel.

In addition, the EQ-5D-5L will be used in this study for economic modeling.

Patients will be requested to complete EQ-5D-5L, the EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, and PRO-CTCAE items at baseline (i.e., Day 1 of Cycle 1) and on Day 1 of each cycle thereafter (see Appendix 1), until and including the study treatment discontinuation visit.

During the survival follow-up, once all treatments are discontinued, all patients will complete only the EORTC IL17 and EQ-5D-5L questionnaires at 3 and 6 months. *Completion of PRO questionnaires will no longer be required after the final OS analysis.*

4.5.9.1 Data Collection Methods for Patient-Reported Outcome Assessments

PRO questionnaire will be self-administered on paper or interviewer-administered (as appropriate) at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, questionnaires will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments that might bias patients' ratings, and prior to the administration of study treatment. For patients who are unable to come into the clinic due to government restrictions or personal safety, PROs may be completed via telephone call; source documentation should be obtained which includes, among other information, that the questionnaires were administered via telephone.

PRO questionnaires, translated into the local language as appropriate, will be completed on paper questionnaires provided by the Sponsor. During clinic visits, PRO questionnaires should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the questionnaires.
- Sites must administer the official version of each questionnaire, as provided by the Sponsor. Questionnaires must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the questionnaires.
- Sites should administer the questionnaires in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the questionnaires.
- Site staff should review all completed questionnaires and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.
- If any of the questionnaires are not completed for any reason, the site staff should report the reason for non-completion in the eCRF.

4.5.9.2 Description of Patient-Reported Outcome Assessment Questionnaires

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 9). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), GHS and QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 module takes approximately 10 minutes to complete. Selected scales (EORTC IL17) will be collected during survival follow up (see Appendix 13).

EORTC QLQ-LC13

The EORTC QLQ-LC13 is a modular supplement to the EORTC QoL questionnaire for use in lung cancer (see Appendix 10). This module incorporates one multiple-item scale to assess dyspnea and a series of single item scales assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All items are using a 4-point scale previously described. The QLQ-LC13 module takes approximately 5 minutes to complete.

Selected Items from EORTC Item Library

In addition, one-item EORTC IL46 will be collected to assess overall side effect impact. The item “To what extent have you been troubled with side-effects from your treatment?” uses the same rating scale of 4 points previously described (see Appendix 10).

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol

Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 11). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for 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 used in this study for informing pharmacoeconomic evaluations.

PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days. Items from the PRO-CTCAE were selected based on their relevance to capture symptoms commonly reported with atezolizumab, cabozantinib, or docetaxel intake and not captured by the EORTC QLQ-C30 and QLQ-LC13. These items capture rash, itching, chills (for IR), musculoskeletal pain, abdominal pain, dysgeusia and neuropathic pain (see Appendix 12).

4.5.10 Optional Tumor Biopsies and Blood Samples

Consenting patients may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Samples collected via resection, core-needle biopsy (at least three cores preferred, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are preferred. 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 Tissue Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

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 biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

For more information on collection of RBR samples see Appendix 2.

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol 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 atezolizumab, cabozantinib, docetaxel, diseases, or drug safety:

- Blood samples collected predose on Day 1 of Cycle 1.

  Although strongly preferred, if sample collection is not feasible predose on Day 1 of Cycle 1, then blood samples may be collected predose on Day 1 of any subsequent cycle visit.
- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy,

esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

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

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

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

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

4.5.10.4 Confidentiality

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

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

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

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients in the experimental arm (Atezo + Cabo) are allowed to discontinue one component of the study treatment but continue to receive the other component as long as the patient is experiencing clinical benefit as determined by the investigator. Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event.
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Patients receiving atezolizumab and cabozantinib: Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease; see Section 4.5.5 for details).
- Patients receiving docetaxel: Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

  For equivocal findings of 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.

4.6.1.1 Post-Treatment Assessments

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment (see Appendix 1). The visit at which response assessment shows PD may be used as the treatment discontinuation visit. Patients who discontinue

study treatment (for any reason) in the absence of radiographic progression (per RECIST v.1.1) will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the patient withdraws consent for follow-up or the Sponsor terminates the study) (see Appendix 1). *After completion of final OS analysis, patients will only need to be followed for 6 months after the last dose of study treatment and information on new anti-cancer therapy will no longer be required. Completion of PRO questionnaires will also no longer be required after the final OS analysis.*

If a patient is discontinued from study treatment because of an adverse event (including adverse events of special interest; see Section 5.2.3) considered to be related to study treatment and the event is ongoing 30 days after the final dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

4.6.2 Patient Discontinuation from the Study

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

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

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study (i.e., survival follow-up), this request must be documented in the 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 and cabozantinib in completed and/or ongoing studies and the most current prescribing information for docetaxel. The anticipated important safety risks are outlined below (see Sections 5.1.1, 5.1.2, and 5.1.3).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Section 4.1) and close monitoring of patients during the study as indicated below. Administration of atezolizumab, docetaxel, and the first dose of cabozantinib 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. Subsequent doses of cabozantinib will be self-administered at home (Section 4.3.2.1). Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 6 for atezolizumab, Appendix 7 for cabozantinib, and local prescribing information for docetaxel. Refer to Sections 5.4 – 5.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

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

5.1.1 Risks Associated with Atezolizumab

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

5.1.2 Risks Associated with Cabozantinib

Cabozantinib has been associated with risks such as the following: GI disorders, non-GI fistula formation, hemorrhage, *venous and arterial thrombotic* events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, *angioedema,* hepatocellular toxicity, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, *musculoskeletal disorders,* and respiratory disorders. Refer to Appendix 7 of this protocol and Section 6 of the Cabozantinib Investigator's Brochure for a detailed description of anticipated safety risks and guidelines for the management of these adverse events associated with cabozantinib.

5.1.3 Risks Associated with Docetaxel

The most common side effects of docetaxel used as a single agent in patients with NSCLC include infections, neutropenia, anemia, thrombocytopenia, peripheral sensory neuropathy, anorexia, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, stomatitis, alopecia, and skin reactions.

For more details regarding the safety profile and management guidelines for adverse events associated with docetaxel, refer to the local docetaxel prescribing information. The investigator may use discretion in adhering to the guidelines, as well as local hospital or clinical practice, considering the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.4 Management of Patients Who Experience Adverse Events and Potential Overlapping Toxicities

Atezolizumab and cabozantinib have molecule-specific safety profiles based on their mechanism of action and adverse events that may overlap. These overlapping adverse events include, but are not limited to, hepatotoxic, endocrine, gastrointestinal, dermatologic, neurologic, renal, and pulmonary events, as well as sign and symptoms such as fatigue and decreased appetite that may be related to multiple system organ class events. The attribution of each drug in certain adverse events may be uncertain when the products are administrated as a combination treatment and warrant diagnostic investigation.

For the management of such potentially overlapping adverse events in patients treated with atezolizumab in combination with cabozantinib, adverse events should be managed according to the recommendation in Appendix 6 (atezolizumab) and Appendix 7 (cabozantinib), applied to the component of the study treatment judged to be the primary cause. If individual component causality for adverse events cannot be adequately determined, conservative management recommendation should be followed to include dose modification/interruption of both agents.

5.1.4.1 Dose Modifications

Atezolizumab

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

Cabozantinib

Dose modifications for cabozantinib are as follows:

- Two dose reduction levels of cabozantinib (20 mg daily, and 20 mg every other day [QOD]) are permitted on the experimental combination arm (see Table 3).
- Dose modification criteria for treatment-related adverse events of cabozantinib are shown in Table 4.
- Dose re-institution and re-escalation after dose interruptions and/or reductions:

  If the patient recovers from his or her toxicities to ≤Grade 1 per NCI CTCAE v.5.0 or to the baseline value (or lower) and the adverse event was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.

If the patient recovers from his or her toxicities to ≤Grade 1 or to the baseline value (or lower) and the adverse event was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose (see Table 4). Patients who initiated treatment with cabozantinib at 40 mg and experience a possibly related adverse event of Grade 1 or 2 severity may be restarted with no dose change after recovery of the toxicities to ≤Grade 1 or to the baseline value (or lower) if appropriate supportive care can prevent or minimize the risk of the adverse event.

Patients receiving a dose of 20 mg QOD on the experimental combination arm who have cabozantinib interrupted may be restarted at the same dose if deemed safe at the discretion of the Investigator. Patients unable to tolerate a dose of 20 mg QOD must discontinue cabozantinib.

Re-escalation to the previous dose may be allowed at the discretion of the investigator but no sooner than 2 weeks beyond resolution of adverse events that led to the dose reduction, which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed following a cabozantinib-related dose reduction for Grade 4 hematologic toxicities or Grade 4 adverse events affecting major organs (e.g., CNS, cardiac, hepatic, renal, pulmonary, GI).

- For patients concurrently taking a strong CYP3A4 inhibitor, reduce the daily cabozantinib dose by 20 mg (e.g., from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.
- For patients concurrently taking a strong CYP3A4 inducer, increase the daily cabozantinib dose by 20 mg (e.g., from 40 mg to 60 mg daily or from 20 mg to 40 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of cabozantinib should not exceed 60 mg.

Table 3 Dose Reduction Levels of Cabozantinib (Oral Dosing)

Assigned Starting Dose	First Dose Level Reduction	Second Dose Level Reduction	Third Dose Level Reduction
40 mg QD (Experimental arm)	20 mg QD	20 mg QOD [a]	No dose reduction permitted

QD = once a day; QOD = once every other day

[a] Cabozantinib will be discontinued if a dose of 20-mg cabozantinib every other day is not tolerated.

Table 4 Dose Modifications for Cabozantinib-Related Adverse Events

CTCAE v.5 Grade	Recommended Guidelines for Management [a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib at the current dose level with supportive care.
Grade 2 AEs which are **intolerable and cannot be adequately managed**	Cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction of cabozantinib and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib must be interrupted immediately. In general, cabozantinib should be discontinued unless the following criteria are met: • Patient is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. • Toxicity can be managed with a dose reduction of cabozantinib following recovery to Grade 1 (or baseline) and optimal medical care. Sponsor must be contacted to discuss treatment continuation upon resolution of AEs.

AE = adverse event.

For guidelines on dose modifications to manage specific adverse events associated cabozantinib treatment, see Appendix 7.

Docetaxel

A single dose reduction of docetaxel is permitted for management of drug-related toxicities (refer to the local docetaxel prescribing information for the recommended dose reduction). After dose reduction, the dose will not be escalated during subsequent administrations. If further dose reduction is indicated, the patient must discontinue docetaxel.

5.1.4.2 Treatment Interruption

Dose interruptions of study treatment may occur at any time and independently at the discretion of the investigator for management of adverse events. If either or both study treatments in the experimental arm are interrupted more than 12 weeks, the Sponsor should be contacted to discuss potential treatment continuation.

Patients on the experimental arm (Atezo + Cabo) will be allowed to discontinue one component of the study treatment but continue to receive the other; the investigator is encouraged to discuss such circumstances with the Sponsor.

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. 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. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

For guidelines on treatment interruption to manage specific adverse events associated with atezolizumab and cabozantinib, see Appendix 6 for atezolizumab and Appendix 7 for cabozantinib.

Docetaxel treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. For guidelines on treatment interruption to manage specific adverse events associated with docetaxel, please refer to the local docetaxel prescribing information.

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed after consultation with the Medical Monitor. The investigator will determine the acceptable length of treatment interruption.

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 patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE;

see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- 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.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, IRRs, CRS, macrophage activating syndrome, hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Grade ≥ 3 diarrhea
- *Myelitis*
- *Facial paresis*

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

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 6):

- 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 6 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 treatment administration and are judged to be related to study treatment infusion (atezolizumab or docetaxel) 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 GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) 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 lung cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). 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 Worsening of Non–Small Cell Lung Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Note: Special situations are not in themselves adverse events but may result in adverse events.

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2). For atezolizumab and cabozantinib, 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

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.

In addition, all special situations associated with atezolizumab and cabozantinib, 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data (from EORTC, PRO-CTCAE items, and EQ-5D-5L questionnaires), and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.3.5.14 Safety Biomarker Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to 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 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 final dose of study treatment (see Section 5.3.1) 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 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 treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, and for 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later. 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, and the infant should have follow up for at least 6 months after birth.

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. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the treatment with atezolizumab in combination with cabozantinib in the experimental arm or during the treatment with docetaxel in the control arm, or 4 months after the final dose of cabozantinib, or 6 months after the final dose of docetaxel. The investigator should

report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy and the infant for at least 6 months after birth. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or 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.

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study should be followed until pregnancy outcome (see Section 5.4.3).

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure
Cabozantinib	Cabozantinib Investigator's Brochure
Docetaxel	Taxotere EMA SmPC

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 the incidence of the above-listed anticipated events 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 Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy, safety, and pharmacokinetics of Atezo + Cabo compared with docetaxel monotherapy in patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* translocation, who have progressed following treatment with platinum-containing chemotherapy and anti–PD-L1/PD-1 antibody, administered concurrently or sequentially.

Efficacy analyses will be performed on the intent-to-treat (ITT) population (i.e., all randomized patients), with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study drug.

Safety analyses will be performed on all randomized patients who received any amount of study drug, with patients grouped according to the actual treatment received. Specifically, a patient will be included in the Atezo + Cabo arm in the safety analyses if the patient receives any amount of atezolizumab or cabozantinib, regardless of the initial treatment assignment at randomization.

Details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before any analysis of the primary endpoint is performed.

6.1 DETERMINATION OF SAMPLE SIZE

The study is designed to test the hypothesis that atezolizumab in combination with cabozantinib prolongs the duration of OS compared to the control arm (docetaxel) in the ITT population.

The sample size determination is based on the number of events required to demonstrate efficacy with regard to OS (as defined in Section 6.4.1) in the ITT population. The estimate of the number of events required is based on the following assumptions:

- 1:1 randomization ratio
- OS curve that follows the exponential distributions
- Two-sided significance level of 0.05 for the comparison of OS
- 90% power to detect an HR of 0.64 in OS in the ITT population, corresponding to an improvement in median OS from 9 to 14.1 months
- One planned interim analysis of OS

  The interim analysis of OS is to be performed when approximately 83% of the total number of OS events required for the final analysis are expected to have occurred. Crossing boundaries are determined based on the Hwang-Shih-DeCani alpha spending function with the gamma parameter of −2.5 (Hwang et al. 1990).
- Accrual duration of approximately 16 months
- Dropout rate of 5% per 24 months for each treatment arm for OS

With these assumptions, approximately 350 patients (approximately 175 per arm) in total will be randomized into the study. The interim OS analysis will be conducted after approximately 182 OS events have occurred. The final OS analysis will be conducted when approximately 220 OS events have occurred, which is expected to occur approximately 28 months after the first patient is enrolled. This number of final OS events corresponds to a minimum detectable difference corresponding to an HR of approximately 0.757.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for discontinuation from the study drug, and reasons for study termination will be summarized by treatment arm. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG performance status, smoking status), will be summarized by treatment arms. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

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

6.4 EFFICACY ANALYSIS

The analysis population for the efficacy analyses will consist of all randomized patients (i.e., the ITT population), with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is OS.

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. The primary endpoint of OS will be compared between treatment arms with the use of the stratified log-rank test. 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 the combination of Atezo + Cabo prolongs the duration of OS relative to the control treatment. The HR and associated 95% CI will be estimated using a stratified Cox proportional hazard model. The stratification factors will be the same as those recorded in the IxRS at randomization (Section 3.1). Results from an unstratified analysis will also be provided.

Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a visual description of the difference between treatment arms. Brookmeyer-Crowley methodology will be used to construct the 95% CI of the median OS for each treatment arm (Brookmeyer and Crowley 1982).

One interim analysis is planned for OS. The timing and stopping boundaries of the OS analyses are described in the sections of sample size determination (Section 6.1) and planned interim analyses (Section 6.10.1).

To assess the consistency of the study results in subgroups defined by demographic (e.g., age, sex, and race/ethnicity) and baseline characteristics (e.g., ECOG Performance Status, histology, and PD-L1 status), the primary efficacy endpoint in these subgroups will be examined. Additional analyses may be performed to evaluate the potential effect of non–protocol-specified anti-cancer therapy on OS. Details of these analyses will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-Free Survival as Assessed by the Investigator

PFS is defined as time from randomization to the first occurrence of disease progression as determined by investigator per RECIST v1.1 or death from any cause (whichever occurs first). Patients who are alive and have not experienced disease progression at

the time of analysis will be censored at the time of last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

Additional analyses may be performed to assess the potential impact of intercurrent events (e.g., missing scheduled tumor assessments) on PFS. Details of these analyses will be provided in the SAP.

The methodologies outlined for the primary analysis of OS will be used for the analyses of PFS by the investigator.

6.4.2.2 Objective Response Rate as Assessed by the Investigator

ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients not meeting these criteria, including patients without any postbaseline tumor assessment, will be considered non-responders. ORR will be analyzed in the randomized patients with measurable disease at baseline.

An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary OS analysis (see Section 6.4.1).

6.4.2.3 Duration of Response as Assessed by the Investigator

DOR will be assessed in patients who had a confirmed objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time from the date of the first occurrence of a confirmed CR or PR (whichever status is recorded first) until the first date that PD or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the OS analysis will be used for the DOR analysis.

6.4.2.4 Time to Confirmed Physical Function or Health-Related Quality of Life Deterioration

Time to confirmed PF or HRQoL deterioration or worsening is defined as the time from the date of randomization to the first date of 10-point or more decrease on either the EORTC QLQ-C30 PF or GHS scale scores (range, 0−100) held for two consecutive assessments, or a 10-point or more score decrease followed by death (any cause) within 21 days or within time till next tumor assessment, whichever occurs first. Confirmed

function or HRQoL deterioration was selected as the event in order to increase the specificity of the endpoints in capturing clinical deterioration due to tumor progression rather than experience of early adverse events that could transiently impact these two concepts.

Patients who do not have a ≥10-point score decrease will be censored at the last assessment date. Patients without a baseline or postbaseline PRO assessment will be censored at the randomization date.

All randomized patients will be included in this time to confirmed deterioration analyses.

The methodologies outlined for the analysis of OS will be used for these analyses.

6.4.2.5 Progression-Free Survival Assessed by Investigator at Landmark Timepoints

The PFS rates at 6 months and 1 year assessed by investigator will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.2.6 Overall Survival Rate at Landmark Timepoints

The OS rates at 1 and 2 years will be estimated using Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method.

6.4.3 Exploratory Efficacy Endpoints

Exploratory analyses of patient-reported function, symptoms, and functions will be detailed in the SAP and will include documentation of scales completion compliance, longitudinal analyses of mean changes in score from baseline, and proportion of patients reporting meaningful changes on each score at each assessment visit, end of treatment, tumor progression, or clinical progression and will be presented by treatment arm. Analyses will be performed in the ITT population.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as all randomized patients who receive any amount of the study drug. Specifically, a patient will be included in the Atezo + Cabo experimental arm in the safety analyses if the patient receives any amount of atezolizumab or cabozantinib, regardless of the initial treatment assignment at randomization.

Safety endpoints will include the incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0, including serious adverse events and

adverse events of special interest, and clinical laboratory results following the administration of study drugs. Drug exposure will be summarized, including duration, dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms and graded according the NCI CTCAE v5.0. All adverse events will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrence of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ADA results, will be summarized by treatment arm. Deaths and causes of deaths will be summarized.

6.5.1 Exploratory Analyses of Patient-Reported Outcome Data

Analyses using PRO data (collected through selected items from the PRO-CTCAE item library and the overall tolerability item) will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. Results from these exploratory analyses will be presented separately from the other safety analyses. PRO data will be analyzed at the item level.

PRO data will be summarized over time including the number and percentage of patients reporting each symptom and the change from baseline at each assessment timepoint, including end of treatment, by treatment arm. In addition, the maximum postbaseline score and change from baseline will be summarized by treatment arm. Details of these analyses will be described in the SAP.

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 2. Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Plasma concentrations of cabozantinib will be collected in this study as outlined in Appendix 2. The concentrations of cabozantinib will be summarized using descriptive statistics as described above.

Additional PK analyses, including population PK and exploratory exposure response analysis, may be conducted, as appropriate, based on the availability of data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment for atezolizumab. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized. Summary of baseline prevalence will be based on patients with at least one evaluable baseline ADA

assessment; summary of postbaseline incidence will be based on treated 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 post-treatment 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).

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

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies. Results from these exploratory biomarker analyses may be reported separately from the CSR.

6.9 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints and will inform pharmacoeconomic models. As such, the data will not be reported in the CSR.

6.10 INTERIM ANALYSES

6.10.1 Planned Interim Analyses

One interim analysis is planned for OS. To control the type I error for OS at two-sided alpha of 0.05, the stopping boundaries for OS interim and final analyses are to be computed with use of the Hwang-Shih-DeCani alpha spending function with the gamma parameter of −2.5 as shown in Table 7.

Table 7 Analysis Timing and Stopping Boundaries for Interim and Final Analyses for Primary Endpoint - Overall Survival

Analysis	Time from FPI (Months)	Information Fraction [a] (No. of Events)	Stopping Boundary HR (p-value [b])
OS IA	23	83% (182)	HR ≤ 0.726 (p ≤ 0.0310)
OS FA	28	100% (220)	HR ≤ 0.757 (p ≤ 0.0396)

FA = final analysis; FPI = first patient in; HR = hazard ratio; IA = interim analysis; No. = number; 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.

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

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 questionnaires will be completed on paper questionnaires provided by the Sponsor. Sites are responsible to ensure that the self- or interviewer-administered questionnaires are complete and accurate and administered prior to receipt of any information that might bias patients' ratings, and prior to the administration of study treatment. If any of the questionnaires is not completed when scheduled for completion,

then the site should report the reason for non-completion in the eCRF. Site will enter the data via EDC system.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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, electronic or 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 study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC), the General Data Protection Regulation (2016/679), 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 MN Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S.

Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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 (see Section 9.6).

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

Study data which may include data on genomic variants may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted CSRs and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

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

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 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 125 sites globally will participate to randomize approximately 350 patients. Screening, enrollment, and treatment assignment will occur through an IxRS.

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

An iDMC will monitor and evaluate patient safety and will review the interim analysis for OS. Tumor response and progression will be evaluated by investigators.

9.5 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.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1 Schedule of Activities

Assessments	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days −28 to −1	Day 1 (every 21 days) (± 3 days)	≤ 30 Days after Final Dose	Survival Follow-Up
Informed consent	x [b]			
Tumor tissue specimens [c]	x			
Demographic data	x			
Medical history, including NSCLC history, PD-L1 status (if available), and baseline conditions [d]	x			
ALK and/or *EGFR* assessment if status is unknown (may be done locally or centrally) [e]	x			
Viral serology [f]	x			
C-reactive protein	x			
Height	x			
Vital signs [g]	x	x [gg]	x [gg]	
Weight	x	x	x	
Complete physical examination [h]	x		x	
Limited physical examination [i]		x [j]		
ECOG Performance Status	x	x [j]	x	
ECG (12-lead)	x [k,i]	x [j, k]		
Hematology [m]	x [l]	x [j, gg]	x [gg]	
Chemistry [n]	x [l]	x [j, gg]	x [gg]	
Pregnancy test [o]	x [l]	x [j, gg]	x [gg]	
Coagulation (INR, aPTT)	x [l]		x [gg]	
TSH, free T3 (or total T3), free T4 [p]	x	x [j, p, gg]	x [gg]	

Appendix 1: Schedule of Activities

Assessments	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days −28 to −1	Day 1 (every 21 days) (± 3 days)	≤ 30 Days after Final Dose	Survival Follow-Up
Urine chemistry including UPCR or 24-hour urine protein	x [l]	x [j]	x	
Urinalysis [r]	x	x [q]	x	
Concomitant medications [s]	x	x [gg]	x [gg]	
Adverse events [t]	x	x [gg]	x [gg]	x
Atezolizumab administration [u]		x		
Cabozantinib dispensing/reconciliation [v]		x		
Docetaxel administration [w]		x		
Patient-reported outcomes [x]		x [y]	x [z]	x [z]
Plasma PK samples for cabozantinib [hh]		See Appendix 2.		
Serum PK samples for atezolizumab [hh]		See Appendix 2.		
Serum ADA samples for atezolizumab [hh]		See Appendix 2.		
PBMC, plasma, and serum samples for biomarkers (central laboratory) [gg, hh]		See Appendix 2.		
Tumor biopsy, if clinically feasible		At time of radiographic progression [aa]		
Optional tumor biopsy at other timepoints [bb]		Any time during study treatment, observation FU or survival FU (at investigator's discretion)		
Tumor response assessments	x [cc]	x [dd, ee]		
Anti-cancer treatment information [ff]			x	x [ff]
Survival follow-up				x [ff]

ADA = anti-drug antibody; Atezo = atezolizumab; Cabo = cabozantinib; CT = computed tomography (scan); ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FFPE = formalin-fixed, paraffin-embedded; FU = follow-up; GHS = global health status; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IL46 = Item List 46; NSCLC = non–small cell lung cancer; MRI = magnetic resonance imaging; OS = overall survival; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life–Core 30 Questionnaire, Version 1.1; QLQ-LC13 = Quality of Life–Lung Cancer 13-Item Questionnaire; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; UPCR = urine protein/creatinine ratio.

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

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

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Representative fresh and archival tumor tissue sample obtained at baseline for exploratory research on biomarkers (e.g., PD-L1 status via central testing), including biomarker assay development. Tumor tissue samples should be submitted before or within 4 weeks of randomization.

[d] If no tissue specimen is available, known PD-L1 status, as defined by a health authority–approved PD-L1 assay, is required.

[e] For patients with nonsquamous NSCLC histology with unknown *EGFR* and/or *ALK* status, test results are required at screening. *EGFR* and/or *ALK* status must be assessed locally or at a central laboratory. If samples are submitted for central testing, additional tissue sample is required. See laboratory manual for details.

[f] At screening, 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.

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

60 minutes prior to the infusion, and, if clinically indicated or if symptoms occurred during the previous infusion, every 15 (±5) minutes during the infusion and at 30 (± 10) minutes after the infusion. Vital signs should be measured prior to docetaxel infusions.

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

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

[j] If screening assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated for Day 1 of Cycle 1. At all cycles subsequent to Day 1 of Cycle 1, laboratory assessments, ECOG Performance Status, ECG (through Cycle 5), and limited physical examination must be performed within 96 hours prior to administration of drug.

[k] ECG recordings will be obtained during screening (within 14 days before initiation of study treatment), on Day 1 of every cycle through Cycle 5, and then as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Specific screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

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

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

[o] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine pregnancy tests will 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.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1, and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

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

[r] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[s] 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.

[t] 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 final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment.

[u] The initial infusion of atezolizumab 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.

[v] Cabozantinib tablets will be given on Day 1 of Cycle 1 after atezolizumab infusion. Patients will take tablets once daily at home thereafter until study treatment is discontinued.

[w] For docetaxel, study drug will be administered according to the local prescribing information, including premedication with steroids.

[x] PRO assessments (EORTC QLQ-C30, EORTC IL17, EORTC QLQ-LC13, EORTC IL46, selected items from the PRO-CTCAE and EQ-5D-5L questionnaires) will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments that could bias patients' rating and the administration of study treatment. Study personnel should confirm all questionnaires for completeness before the patient leaves the investigational site.

[y] Patient-completed questionnaires should be completed by the patients prior to any assessments, tests or interactions that might bias patients' view on their health status.

[z] PRO assessments (EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, selected items from the PRO-CTCAE, and EQ-5D-5L) will be completed at the post treatment follow up visit. *Completion of PRO questionnaires will no longer be required after the final OS analysis.*

[aa] Patients will undergo a tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[bb] Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.10 for details.

[cc] 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. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening assessments must include CT scans (with oral or IV contrast) of chest, abdomen, and pelvis, as wells as a CT scan (with oral or IV contrast) or MRI of the head. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest must be performed and MRI scans of the abdomen, pelvis, and head must be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At subsequent (post-screening) tumor assessments, patients with a history of irradiated brain metastasis at screening are not required to undergo brain scan unless clinically indicated. The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used to assess disease sites at screening should be used for subsequent tumor assessments. Bone scans and CT scans of the neck should also be performed at screening, if clinically indicated.

[dd] All patients will undergo tumor assessments at baseline, every 6 weeks (±7 days) for the first 48 weeks following Day 1 of Cycle 1, and every 9 weeks (±7 days) after completion of the Week 48 tumor assessment regardless of treatment delays. Patients will continue scanning regardless of treatment delays until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients in the experimental arm who are treated beyond disease progression per RECIST v1.1 will continue to undergo tumor assessments at the frequency described above until (i.e., every 6 weeks [±7 days] for the first 48 weeks and every 9 weeks [± 7 days] after 48 weeks) until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[ee] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[ff] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (every 12 weeks [±7 days]) or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). *After completion of final OS analysis, patients will only need to be followed for 6 months after the last dose of study treatment and information on new anti-cancer therapy will also no longer be required.* If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[gg] For patients in either arm at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the patient's home or another suitable location.

[hh] *On the basis of emerging safety, activity, or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. After final OS analysis is conducted, the Sponsor may decide to no longer collect additional biomarker samples. The existing collected samples may still be used for exploratory analysis.*

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Experimental Arm (Atezo + Cabo)	Control Arm (Docetaxel)
Day 1 of Cycle 1	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum) • Biomarker (blood for RBR, optional [a])	• Biomarker (PBMC, plasma, serum) • Biomarker (blood for RBR, optional [a])
Day 1 of Cycle 1	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)	
Day 1 of Cycle 2	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum)	• Biomarker (PBMC, plasma, serum)
Day 1 of Cycle 3	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 4	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Cabozantinib PK (plasma) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)

Appendix 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Experimental Arm (Atezo + Cabo)	Control Arm (Docetaxel)
Day 1 of Cycle 5	Predose (same day as treatment administration)	• Cabozantinib PK (plasma)	
Day 1 of Cycle 8	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 12	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Day 1 of Cycle 16	Predose (same day as treatment administration)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)	• Biomarker (plasma, serum)
Post-treatment follow-up visit (≤ 30 days after final dose)[c]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (PBMC, plasma, serum)	• Biomarker (PBMC, plasma, serum)
Disease Progression [c]	At time of radiographic progression per RECIST v1.1 [b]	• Biomarker (PBMC, plasma, serum)	• Biomarker (PBMC, plasma, serum)

Appendix 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

ADA = anti-drug antibody; Atezo = atezolizumab; Cabo = cabozantinib; eCRF = electronic Case Report Form; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Notes: 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.

On the basis of emerging safety, activity, or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. After final OS analysis is conducted, the Sponsor may decide to no longer collect additional biomarker samples. The existing collected samples may still be used for exploratory analysis.

Blood sampling for cabozantinib PK analyses: After Day 1 of Cycle 1, PK samples should be collected approximately 8 or more hours after the previous dose of cabozantinib, and if cabozantinib will be administered on that day, PK samples should be collected prior to cabozantinib administration. The investigator will ask the patient for the date and time of the most recent prior dose of cabozantinib, and this information will be recorded on the appropriate eCRF.

[a] 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. RBR samples are preferred to be collected on Day 1 of Cycle 1; however, they may be collected predose on Day 1 of any subsequent cycle visit.

[b] Blood collections should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[c] For patients in either arm at participating sites who have provided written informed consent to participate in mobile nursing visits, collection of this sample may be performed by a trained nursing professional at the patient's home or another suitable location.

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 the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, 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 $\geq$ 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 × 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 at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

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

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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

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

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

REFERENCES

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

Appendix 4
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-mediated 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 • Granulomatosis *with polyangiitis*

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

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

PROCEDURES

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

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

Appendix 6
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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 for a given patient 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 patients with atezolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

For information on dose modification, see Section 5.1.4.1.

TREATMENT INTERRUPTION

For information on treatment interruption, see Section 5.1.4.2.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Event	Management
	• 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.
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 event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before 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 or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume 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 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 test.

[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.

[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.

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 and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume 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)

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

GI = gastrointestinal.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before 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 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • 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 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.*
Grade 3 and 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]

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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 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 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. • 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.

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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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 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 and convert to 1–2 mg/kg/day oral prednisone or equivalent 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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • 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.

[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 CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., 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, 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, or VAD *or pericardiocentesis* as appropriate. • 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.

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 of atezolizumab may receive premedication with *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 during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Severe 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.)

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.)

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 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 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) for information on experimental treatments for CRS.

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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 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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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-limited, 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]
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.

Event	Management
	• Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

[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.

[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.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. 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.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • 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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before 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-MEDIATED MENINGOENCEPHALITIS

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

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

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

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

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

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 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]

Table 13 Management Guidelines for Renal Events

Event	Management
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.

[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 the Medical Monitor. [c]

[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 $\leq$10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to the equivalent of $\leq$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.

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

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, Grade 4	• 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.

[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.

[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.

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 $\geq 38.5°C$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) 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 $\leq 181 \times 109$/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.

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Appendix 7
Risks Associated with Cabozantinib and Guidelines for Management of Adverse Events Associated with Cabozantinib

This appendix provides guidelines for management of patients who experience cabozantinib-associated adverse events (e.g., GI disorders, hemorrhage, thromboembolic events, hypertension, osteonecrosis, proteinuria, hepatocellular toxicity, blood system disorders, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders). *Appendix 6 describes risks associated with atezolizumab and provides guidelines for management of patients who experience atezolizumab-associated IRRs and immune-mediated adverse events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, myocarditis, pericardial disorders, pancreatic, dermatologic, neurologic, meningoencephalitis, renal, myositis, hemophagocytic lymphohistiocytosis).*

DOSE MODIFICATIONS

For information on dose modification, see Section 5.1.4.1.

TREATMENT INTERRUPTION

For information on treatment interruption, see Section 5.1.4.2.

MANAGEMENT GUIDELINES

The most frequent adverse events experienced by ≥20% of patients treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, palmar-plantar erythrodysesthesia syndrome, weight decreased, vomiting, hypertension, constipation, asthenia, dysphonia, and *AST increased*. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator Brochure.

Other medically important but less frequent adverse events include arterial *and venous* thrombotic adverse events (e.g., DVT, pulmonary embolism, TIA, *arterial aneurysm*, and myocardial infarction), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, *rhabdomyolysis*, and reversible posterior leukoencephalopathy syndrome (RPLS; preferred term: posterior reversible encephalopathy syndrome [PRES]).

Adverse events associated with laboratory test abnormalities that were experienced by ≥ 5% of cabozantinib-treated patients in descending order of frequency were *AST increased, ALT increased, anemia, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, proteinuria, hypophosphatemia, ALP increased, LDH increased, neutropenia, lipase increased, hyponatremia, platelet count decreased, GGT increased, hypoalbuminemia, leukopenia, and blood TSH increased.*

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPE, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (see Section 5.1.4.1).

Cabozantinib should be discontinued for the following adverse events: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, *hypertension with life-threatening consequences*, persistent uncontrolled hypertension despite optimal medical management, *serious and life-threatening rhabdomyolysis,* and RPLS.

GASTROINTESTINAL DISORDERS

Gastrointestinal (GI) perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, patients should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue cabozantinib and initiate appropriate management in patients who have been diagnosed with GI perforation or fistula.

Diarrhea: Patients should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 1. Administration of antidiarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some patients may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per Investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be

performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 1 Management of Diarrhea Associated with Cabozantinib

Status	Management
Tolerable Grade 1–2 (duration < 48 h)	• Continue with study treatment and consider dose reduction. • Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). • Dietary modifications (e.g., small lactose-free meals, bananas and rice). • Intake of isotonic fluids (1–1.5 L/day). • Re-assess after 24 hours: – Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval. – Diarrhea not resolving: Continue/resume antidiarrheal treatment.
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment. • Ask patient to attend clinic. • Rule out infection (e.g., stool sample for culture) – Administer antibiotics as needed (e.g., if fever or Grade 3–4 neutropenia persists > 24 h) • Administer fluids (1–1.5 L/day orally or. IV, as appropriate) for hydration or to correct electrolyte abnormalities. • For Grade 3-4 or complicated lower-grade diarrhea consider hospitalization and IV hydration. • Re-assess after 24 h – Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose. – Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist.

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (see Section 4.4 for further details).

NON-GASTROINTESTINAL FISTULA

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in patients undergoing treatment with VEGF pathway inhibitors.

Discontinue cabozantinib and initiate appropriate management in patients who have been diagnosed with a non-GI fistula.

HEMORRHAGE

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Patients should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated patients with brain metastases has not been thoroughly analyzed. Patients enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be discontinued in patients with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

THROMBOEMBOLIC EVENTS

Thromboembolic events are frequent in cancer patients due to procoagulant changes induced by the malignancy or anti-cancer therapy. Deep vein thrombosis (DVT) and pulmonary embolism (PE) have been observed in clinical studies with cabozantinib, including fatal events. Patients who develop a PE and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in patients with PE or DVT if it is determined that the event is uncomplicated and that the patient is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per the discretion of the Investigator and according to individual protocols. Low-molecular weight heparin (LMWH) or anticoagulation with direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban is allowed for the treatment of thromboembolic events if clinically indicated and the benefit outweighs the risk per the investigator's discretion. Anticoagulation with warfarin or other coumarin-related agents, or the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor betrixaban, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines is not allowed. Refer to Sections 4.1.2 and 4.4.1 for detailed information regarding the use of anti-coagulants.

Arterial thrombotic events (e.g., TIA, myocardial infarction) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in

patients who develop an acute myocardial infarction, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

The available cabozantinib data from clinical studies and postmarketing experience showed that arterial aneurysms and dissections may occur rarely during cabozantinib treatment. These events appear to primarily occur in the presence of hypertension (which is a known risk factor for this condition); however, in some events the presence of hypertension was not documented. Discontinuation of treatment with cabozantinib should be considered in subjects who develop aortic aneurysm and dissections.

HYPERTENSION

Table 2 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in patients with *hypertension with life-threatening consequences or when urgent intervention is indicated, and appropriate medical management should be initiated.*

Table 2 Management of Hypertension [a] Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
≥140 mm Hg (systolic) and < 160 mm Hg OR *≥90* mm Hg (diastolic) and *<100* mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP *<140* mm Hg systolic *or <90* mm Hg diastolic. • If patient is symptomatic, *cabozantinib treatment should be interrupted and can only be restarted once symptoms have resolved and BP is < 140 mm Hg systolic and < 90 mm Hg diastolic.*

Table 2 Management of Hypertension [a] Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
≥ 160 mm Hg (systolic) OR ≥ *100* mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per Investigator discretion. • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or sustained diastolic BP > *100* mm Hg, or if patient is symptomatic. • *Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor patient closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 160 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted.* • Restart cabozantinib treatment at the *reduced* dose and re-escalate only if BP falls to and is sustained at < *140* mm Hg systolic and < *90* mm Hg diastolic.
Hypertension with life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	• Discontinue cabozantinib treatment. • *Initiate appropriate medical management.*

BP = blood pressure.

[a] The Investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >*140* mm Hg or diastolic BP > *90* mm Hg based on their clinical judgment and assessment of the individual patient.

STOMATITIS AND MUCOSITIS

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence, which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the patient is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysesthesia (PPE; also known as hand-foot syndrome): Skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All patients on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPE are summarized in Table 3.

Table 3 Management of Hand-Foot Syndrome (PPE) Associated with Cabozantinib

CTCAE v5 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level. [a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume cabozantinib at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue the patient from study treatment if PPE does not improve within 6 weeks.

CTCAE = Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug; PPE = palmar-plantar erythrodysesthesia-.

[a] Permitted dose levels are defined by individual protocols.

ANGIOEDEMA

Angioedema should be managed according to standard practice. The patient should be observed until symptoms resolve, with particular attention to maintaining an open airway.

OSTEONECROSIS

Osteonecrosis has been reported in patients treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Advise patients regarding oral hygiene practice and to quickly report symptoms to the Investigator. Caution should be used in patients receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

If ONJ occurs, cabozantinib treatment should be held and should not be restarted until the condition has sufficiently healed and the Sponsor has approved the re-initiation of therapy.

PROTEINURIA

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 4 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in patients who develop nephrotic syndrome (proteinuria $>$3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 4 Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring.
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days. • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR >2 mg/mg on repeat UPCR testing or urine protein >2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if repeated UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if repeated UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose *hold unless otherwise approved by Sponsor.* • *Repeat UPCR within 7 days and once per week. If UPCR <1 mg/mg on two consecutive readings, UPCR monitoring can revert to protocol-specific times (second reading is confirmatory and can be done within 1 week of first reading). If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.*
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• *Hold* cabozantinib treatment pending repeat UPCR monitoring within 7 days and/or 24-h urine protein. • If ≥3.5 mg/mg on repeat UPCR monitoring, continue to *hold* cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and *monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to <1 mg/mg. If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.*
Nephrotic syndrome	• Discontinue cabozantinib treatment.

UPCR = urine protein/creatinine ratio.

NERVOUS SYSTEM DISORDERS

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory

impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with RPLS.

HEPATOCELLULAR TOXICITY

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that patients with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in patients who develop increased values of ALT, AST, or bilirubin and other causes (e.g., cancer-related, or infection) should be evaluated.

Management guidelines for hepatotoxicity related to cabozantinib treatment are provided in Table 5.

Table 5 Management of Hepatotoxicity Associated with Cabozantinib

Severity of Transaminase (ALT or AST) Elevations by CTCAE	Treatment/Cabozantinib Dose Modification
Grade 1	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and adding supportive care as indicated.
Grade 2	• Interrupt cabozantinib *if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin*. • Restart cabozantinib, at the same dose or a reduced dose at Investigator discretion, after laboratory abnormalities have resolved to no higher than CTCAE Grade ≤ 1 or baseline grade.
Grade ≥ 3	• Interrupt cabozantinib and consider more frequent monitoring of ALT and/or AST. • Restart cabozantinib at a reduced dose after laboratory abnormalities have resolved to CTCAE Grade ≤ 1 or baseline grade. • Discontinue if laboratory abnormalities cannot be reversed despite interruption of cabozantinib.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events.

Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors.

The following condition requires discontinuation of cabozantinib:

- Drug-related ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN without reasonable other explanation, consistent with drug-induced liver injury.

INFECTIONS AND INFESTATIONS

Infections are commonly observed in cancer patients. Predisposing risk factors include decreased immune status (e.g., after myelosuppressive anti-cancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.

BLOOD AND LYMPHATIC SYSTEM DISORDERS

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Patients with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. However, for patients with thrombocytopenia, dose modifications should be followed in accordance to Table 3 in Section 5.1.4.1.

Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

FATIGUE

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease-specific morbidities have been excluded when not prohibited.

WEIGHT LOSS

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

CORRECTED QT PROLONGATION

The effect of orally administered cabozantinib 140 mg QD on QTc interval was evaluated in a placebo-controlled study in patients with medullary thyroid cancer. A mean increase in QTcF of 10–15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated patients in this study had a QTcF >500 ms. Review of the larger safety database *(approximately 11,000 patients exposed to cabozantinib in clinical trials and*

more than 98,000 patients in the postmarketing setting) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value >500 ms or an increase of >60 ms above baseline per the site's ECG read, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is >500 ms or the average increase is >60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment.
- Immediately notify the Sponsor.
- Hospitalize symptomatic patients (e.g., with palpitations, dizziness, syncope, orthostatic hypotension), or those with a significant ventricular arrhythmia on ECG for a thorough cardiology evaluation and management.
- Consider cardiology consultation for asymptomatic patients for evaluation and management.
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org).
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms and the average increase is ≤ 60 ms above baseline, or a consulting cardiologist or appropriate expert determines that the frequency of ECGs may revert to the schedule in the protocol.

Patients with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted but only at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms or increase of ≤ 60 ms above baseline
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved

- Sponsor *has reviewed all available information and has agreed to the continuation of study treatment*

Following re-initiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined timepoints.

Cabozantinib treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation *(confirmed by central ECG lab)* after re-initiation of study treatment at a reduced dose

ENDOCRINE DISORDERS

Thyroid dysfunction, primarily hypothyroidism, has been observed with cabozantinib treatment. The underlying potential mechanism of thyroid dysfunction observed with cabozantinib treatment remains unclear. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and approved by the Sponsor. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

RESPIRATORY DISORDERS

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation and pneumonia have been reported in subjects

treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

ELECTROLYTE DISORDERS

Serum electrolyte imbalance including hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia has been reported during treatment with cabozantinib. *In some cases, there have been Grade 3 or 4 and/or serious.*

There are many causes for an electrolyte imbalance including loss of body fluids (e.g., from prolonged vomiting or diarrhea), inadequate diet, kidney disease, and use of certain concomitant medications (e.g., diuretics). Electrolyte imbalance may create a variety of symptoms (e.g., weakness, fatigue, confusion, muscle spasm, constipation, and irregular heartbeat).

Serum electrolyte levels should be monitored closely while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines (see Section 5.1.4.1, Table 4) and may include oral or IV replacement.

REFERENCES

Turnage RH, Badgwell B. Abdominal wall, umbilicus, peritoenum, mesentery, omentum and retroperitoneum. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston Textbook of Surgery. 20th ed. 2016.

Appendix 8
Highly Effective Methods of Contraception

In Inclusion Criteria (see Section 4.1.1), sexually active fertile patients and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and until the end of relevant systemic exposure, defined as 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later , for women, and 4 months after the final dose of cabozantinib, or for 6 months after the final dose of docetaxel.

The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as "effective methods of contraception," they should be used together with another method.

Contraception guidance for female patients of childbearing potential

One of the highly effective methods of contraception listed below, in combination with one acceptable barrier method below, is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the final dose of atezolizumab and/or 4 months after the final dose of cabozantinib, whichever is later. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly effective contraceptive methods that are user dependent: These methods have a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral or injectable

Highly effective contraceptive methods that are user independent:

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine hormone-releasing system
- Intrauterine device
- Bilateral tubal occlusion

- Vasectomized partner
  - A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female patient of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used
- Sexual abstinence
  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

    It is not necessary to use any other method of contraception when complete abstinence is elected.

    Female patients of childbearing potential who choose complete abstinence must continue to have pregnancy tests per the protocol. Acceptable alternate methods of highly effective contraception must be discussed in the event that any of these patients chooses to forego complete abstinence.

<u>Acceptable barrier methods for use in combination with a highly effective method:</u>

- Male or female condom with or without spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide

<u>Unacceptable as a Sole Method of Contraception:</u>

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception of which inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods)
- Withdrawal (e.g., coitus interruptus)
- Spermicide only
- Lactation amenorrhea method

Contraception guidance for male participants with partner(s) of childbearing potential

Male patients with female partners of childbearing potential are eligible if they agree to the following during the course of study treatment and until the end of relevant systemic exposure, defined as 4 months after the final dose of cabozantinib, or for 6 months after the final dose of docetaxel.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male patients must refrain from donation sperm and are required to use a condom to prevent transmission of study treatment in semen during the treatment period and for 4 months after the final dose of cabozantinib.

  Note: Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile during the treatment period and for 4 months after the final dose of cabozantinib.

- Docetaxel may alter male fertility. Male patients randomly assigned to receive docetaxel should seek advice on conservation of sperm prior to treatment.

Appendix 9
European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 10
European Organisation for Research and Treatment of Cancer Quality of Life–Lung Cancer 13-Item Questionnaire: EORTC QLQ-LC13

Additional item

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**
To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 11
EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

English version for the USA

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

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

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

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

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

PAIN / DISCOMFORT

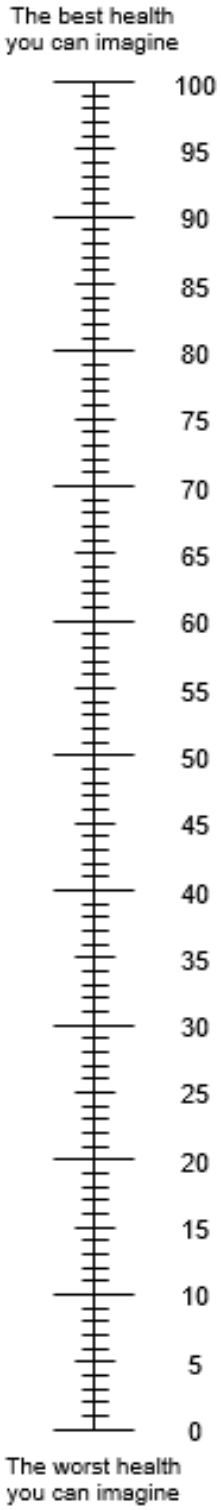
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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

YOUR HEALTH TODAY = ☐



Appendix 12
Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

4.	In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

6.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Appendix 13
European Organisation for Research and Treatment of Cancer
Item List 17 Questionnaire: EORTC IL17

ENGLISH

EORTC IL17

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
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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