Official Title: An Open-Label, Phase IIIb, Single-Arm, Multicenter Study of Atezolizumab Plus Nab-Paclitaxel in the Treatment of Unresectable Locally Advanced or Metastatic PD-L1-Positive Triple-Negative Breast Cancer

NCT Number: NCT04148911

Document Date: Protocol Amendment Version 6: 10-Nov-2023

PROTOCOL

PROTOCOL TITLE:	**AN OPEN-LABEL, PHASE IIIb, SINGLE-ARM, MULTICENTER STUDY OF ATEZOLIZUMAB PLUS NAB-PACLITAXEL IN THE TREATMENT OF UNRESECTABLE LOCALLY ADVANCED OR METASTATIC PD-L1–POSITIVE TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	MO39874
STUDY NAME:	EL1SSAR
VERSION NUMBER:	6
TEST PRODUCT:	Atezolizumab (RO5541267)
STUDY PHASE	Phase IIIb
REGULATORY AGENCY IDENTIFIER NUMBERS:	EudraCT Number: 2019-002488-91 NCT Number: NCT04148911
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
6	See electronic date stamp on the final page of this document.
5	22 February 2023
4	20 February 2022
3	8 February 2021
2	13 February 2020
1	30 July 2019

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol MO39874 (EL1SSAR), Version 6, has been primarily amended to update the adverse event management guidelines to align with the Atezolizumab Investigator's Brochure, Version 20. Substantial changes to the protocol, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with Clinical Trials Regulation and other guidelines.
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.2).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 8).

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 TITLE:	**AN OPEN-LABEL, PHASE IIIb, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) PLUS NAB-PACLITAXEL IN THE TREATMENT OF UNRESECTABLE LOCALLY ADVANCED OR METASTATIC PD-L1–POSITIVE TRIPLE-NEGATIVE BREAST CANCER**
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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

PROTOCOL TITLE:	**AN OPEN-LABEL, PHASE IIIb, SINGLE-ARM, MULTICENTER STUDY OF ATEZOLIZUMAB PLUS NAB-PACLITAXEL IN THE TREATMENT OF UNRESECTABLE LOCALLY ADVANCED OR METASTATIC PD-L1–POSITIVE TRIPLE-NEGATIVE BREAST CANCER**
REGULATORY AGENCY IDENTIFIERS:	EudraCT Number: 2019-002488-91 NCT Number: NCT04148911

STUDY RATIONALE

The primary aim of this study is to evaluate the safety of atezolizumab plus nab-paclitaxel in patients with PD-L1-positive unresectable locally advanced or metastatic triple-negative adenocarcinoma of the breast (TNBC) who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC. The study will also evaluate treatment efficacy.

OBJECTIVES AND ENDPOINTS

Objectives	Corresponding Endpoints
Primary Safety Objective:	
To evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	**Primary Safety Endpoints**: • Incidence of treatment-emergent Grade ≥ 3 AEs • Incidence of treatment-emergent Grade ≥ 2 imAEs [1]
Secondary Safety Objective:	
To further evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	**Secondary Safety Endpoints**: • Incidence of all treatment-emergent AEs • Incidence of treatment-emergent SAEs
Secondary Efficacy Objectives:	
To evaluate the effect of atezolizumab plus nab-paclitaxel on key survival outcomes in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• OS, defined as the time from initiation of study treatment to death from any cause (analyzed in the ITT population, and in the subset of patients with centrally confirmed PD-L1-positive tumor status) • PFS, defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first (analyzed in the ITT population, and in the subset of patients with centrally confirmed PD-L1-positive tumor status). PFS will be assessed by the investigator according to RECIST v1.1.

Abbreviations: AE=adverse event; imAE=immune-mediated adverse event; OS=overall survival; PD-L1=Programmed death-ligand 1; PFS=Progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TNBC=triple-negative breast cancer; v=version

[1] Immune-mediated adverse events (imAEs) are events that resemble autoimmune diseases, and are known side effects of immune checkpoint inhibitors, including atezolizumab

OVERALL DESIGN AND STUDY POPULATION

This phase IIIb, open label, single arm, study will evaluate the safety and efficacy of atezolizumab plus nab-paclitaxel in the treatment of unresectable locally advanced or metastatic PD-L1-positive TNBC.

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

Phase:	Phase IIIb	**Population Type:**	Adult patients
Control Method:	None	**Population Diagnosis or Condition:**	Unresectable locally advanced or metastatic PD-L1-positive TNBC patients who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC
Interventional Model:	Single group	**Population Age:**	≥18 years of age
Test Product{s}:	Atezolizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Treatment Assignment Method:**	Not applicable
Number of Arms:	One	**Number of Participants to Be Enrolled:**	Approximately 180 patients

STUDY TREATMENT

Atezolizumab will be administered at a dose of 840 mg via IV infusion on Days 1 and 15 of every 28-day treatment cycle. Nab-paclitaxel will be administered at the 100 mg/m2 dose via 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle (3-weeks-on, 1-week-off schedule). No dose modification of atezolizumab is allowed.

DURATION OF PARTICIPATION

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1, unacceptable toxicity, or until end of study.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee (periodical review of safety data)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibodies
anti-HBc	antibody against the hepatitis B core antigen
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BC	breast cancer
BUN	blood urea nitrogen
CAP	College of American Pathologists
CD	cluster of differentiation
CI	confidence Interval
CL	confidence Limit
CNS	central nervous system
CCOD	Clinical Cut Off Date
[redacted]	
COPD	chronic obstructive pulmonary disease
[redacted]	
COVID–19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DFS	disease-free survival
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation	Definition
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOS	end of study
ER	oestrogen-receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	fixed formalin paraffin embedded
G-CSF	granulocyte colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HR^+ BC	hormonal-receptor-positive breast cancer
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IL-2	interleukin-2
imAE	immune-mediated adverse event
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in situ hybridisation
ITT	intent to treat

Abbreviation	Definition
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice/web response system
LDH	lactate dehydrogenase
LFT	liver function test(s)
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
mBC	metastatic breast cancer
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-investigational medicinal products
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PARP	Poly (ADP-ribose) polymerase
PCR	polymerase chain reaction
PD-1	programmed cell death–protein 1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone-receptor
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
Q1W	every week (weekly)
Q2W	every 2 weeks
Q3W	every 3 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Steering Committee

Abbreviation	Definition
SCAR	severe cutaneous adverse reaction
SCLC	small cell lung cancer
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase (AST)
SGPT	serum glutamic-pyruvic transaminase (ALT)
SITC	Society for Immunotherapy of Cancer
STD	standard deviation
TC	tumor cell
TFI	treatment-free interval
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
T3	triiodothyronine
T4	thyroxine
ULN	upper limit of normal
U.S./USA	United States of America
v	Version
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

1.1.1 Epidemiology

Breast cancer (BC) is the second most common cancer in the world and by far the most frequent cancer among females, both in more and less developed regions (Torre et al. 2017; Bray et al. 2018; Ferlay et al. 2018; Feng et al. 2019). There were an estimated 1.67 million new cancer cases diagnosed worldwide in 2012 (25% of all cancers) (age-adjusted incidence rates per 100,000 population) are highest North America (91.6%), followed by Europe (69.9%), Latin America (47.2%), and Eastern Asia (27.0%) (Ferlay et al. 2013). In the United States, there was a statistically significant increase of 0.4% (95% confidence interval [CI]: 0.1% to 0.8%) per year between 2009 and 2014 in the incidence of BC (Jemal et al. 2017), and it is projected that there will be 255,180 new diagnoses due to BC (Siegel et al. 2017). An estimated 3,560,570 women were living with BC in the United States in 2016 (Miller et al. 2016). In Europe, BC accounts for 28.8% of female cancers and is estimated to affect more than one in 10 women (Lundqvist et al. 2016). In five Latin American countries, the estimated incidence rate for BC was between 27.2 and 74.0 per 100,000 women in 2008 (Nigenda et al. 2016). The majority of patients are diagnosed with localized BC; however, approximately 6% of patients present with de-novo metastatic disease and between 10% and 40% of patients with localized BC will relapse systemically (Zeichner et al. 2015a, 2015b).

BC ranks as the fifth leading cause of death from cancer overall in the world (522,000 deaths or 6.6% of all cancer-related deaths). It is the leading cause of cancer-related deaths in women (14.7% of all cases) and is the second cause of cancer death in women in more developed regions (198,000 deaths; 15.4% of total) after lung cancer (Ferlay et al. 2015, 2018; Torre et al. 2015). Age-adjusted mortality rates (per 100,000 population) are highest in Europe (16.1), followed by North America (14.8), Latin America (13.0), and Eastern Asia (6.1) (Ferlay et al. 2013). In the United States, the death rate due to BC decreased by 1.6% (95% CI: –1.8% to –1.4%) per year between 2009 and 2014 (Jemal et al. 2017), and it is projected that there will be 41,070 deaths due to BC in 2017 (Siegel et al. 2017). The 5-year relative survival rates for BC cases diagnosed between 2006 and 2012 were 90.8% (95% CI: 90.5% to 91.1%) (Jemal et al. 2017). In five Latin American countries, the estimated mortality rates for BC were between 10.0 and 20.1 per 100,000 women in 2008 (Nigenda et al. 2016).

The above statistics include all subtypes of BC. However, BC is a heterogeneous disease encompassing about 15 different types of carcinomas, which are for therapeutic reasons, further classified according to their estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (Brouckaert et al. 2012). Such subgroups have important implications for the choice of therapy, treatment outcomes, recurrence rate, and mortality risk. The lack of expression of ER, PR, and HER2 is referred to as triple-negative BC (TNBC) (Trivers et al. 2009; Zeichner et al. 2016).

The prognosis of patients with metastatic breast cancer (mBC) varies from several months to many years depending upon multiple factors, including, but not limited to, ER/PR status and HER2 status (Zeichner et al. 2015a, 2015b). Between 1975 and 1977 and 2006 and 2012, the 5-year relative survival for distant-stage BC increased from 18.7% (95% CI: 16.9% to 20.6%) to 33.6% (95% CI: 32.2% to 35.0%) for female BC (Jemal et al. 2017). However, most new treatment options for mBC are only effective for ER/PR-positive or HER2-positive metastatic tumors (Zeichner et al. 2016).

1.1.2 Metastatic Triple-Negative Breast Cancer (TNBC)

The triple-negative subtype is a heterogeneous group of BCs characterized by the lack of expression of hormonal receptors and the absence of HER2 overexpression (Collignon et al. 2016). According to the St. Gallen International Expert Consensus (Goldhirsch et al. 2009) and the recommendations of the American Society of Clinical Oncology and the American College of Pathology (Hammond et al. 2010; Allison et al. 2020), tumor specimens are ER or PR negative if less than 1% of tumor cells express the estrogen and progesterone receptors via immunohistochemistry (IHC), and HER2 negative if showing IHC 0 or 1+ or in situ hybridization (ISH) negative using single-probe ISH or dual-probe ISH (Wolff et al. 2018). Should these definitions be revised by clinical experts during the study, the updated definitions may be adopted as part of a protocol amendment.

Approximately 15%–20% of all BCs belong to the triple-negative phenotype that has distinct risk factors, distinct molecular features, and a particular clinical presentation and outcome (Brouckaert et al. 2012; Lin et al, 2012; Penault-Llorca and Viale 2012). The TNBC phenotype has been associated with Black race, younger age, and more advanced tumor stage at presentation (Millikan et al. 2008; Lund et al. 2009; Trivers et al. 2009; Lin et al. 2012; Danforth 2013). TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBC exhibit rapid progression and a poor clinical outcome (Mersin et al. 2008; Trivers et al. 2009; Wahba and El-Hadaad, 2015). TNBC is associated with a higher risk of brain or lung metastases (Lin et al. 2012) and have worse breast cancer-specific and overall survival (OS) (Lin et al. 2012); median OS is generally between 13 months (Kassam et al. 2009) and 17.5 months in patients treated with various chemotherapy agents (Roche data on file).

Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBCs and their diverse gene-expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies (Hirshfield and Ganesan 2014). Chemotherapy is the mainstay of treatment of TNBC, and current treatment strategies for triple-negative disease include anthracyclines, taxanes, ixabepilone, platinum agents, and bevacizumab (Hudis and Gianni 2011). Chemotherapy has been the only active treatment for metastatic TNBC for a long time; however, this scenario has recently changed with the

approval and incorporation of poly (ADP-ribose) polymerase (PARP) inhibitors, checkpoint-mediated immune modulation, and antibody-drug conjugates (Adalms et al, 2019; Emens et al. 2015; Schmid et al. 2017; Caparica et al. 2019; Bardia et al. 2021; McArthur HL, 2021).

1.1.3 Treatment of Metastatic Breast Cancer

The treatment algorithm for patients with mBC is based on several factors that include clinical, pathologic, and histologic characteristics, such as the presence or absence of HER2 amplification, hormone receptor status, and prior response to and/or failure of hormonal agents; number and specific sites of metastatic disease; and treatment history in both the metastatic and adjuvant settings (Piccart-Gebhart et al. 2008). Treatment options for mBC include endocrine therapies, monoclonal antibodies, antibody–drug conjugates, targeted therapies, and different types of chemotherapy (Hernandez-Aya and Ma 2016). Several cytotoxic chemotherapy agents have shown activity in mBC, including anthracyclines, taxanes, gemcitabine, capecitabine, vinorelbine, eribulin, and ixabepilone. The response rates and progression-free intervals observed with these agents vary depending on the extent and type of prior therapy and extent of metastatic disease, as well as the biology of the disease. In general, anthracycline-based combination therapy and taxanes such as paclitaxel and docetaxel are believed to show the greatest activity (Piccart-Gebhart et al. 2008). Given the use of regimens containing anthracyclines in the adjuvant setting and the risk of cardiotoxicity associated with repeated courses, taxanes are now the most commonly used agent for patients with locally advanced or metastatic disease, particularly in the front-line setting (Greene and Hennessy 2015). However, although TNBC may respond to chemotherapy, including taxanes, relatively few new agents have been approved for the subset of patients with mTNBC (Carey et al. 2012; O'Shaughnessy et al. 2014; Hirshfield and Ganesan, 2014; Zeichner et al. 2016). Approval for atezolizumab for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 has been granted in the European Union (EU) and in several other countries globally.

1.1.3.1 PD-L1 Inhibitors in the Treatment of TNBC

Investigations of targeted therapy for advanced TNBC includes immune checkpoint inhibitors targeting the PD-1/PD-L1; also called B7-H1 or cluster of differentiation [CD]274). PD-L1 is expressed in many cancer and immune cells (ICs; e.g., macrophages), and plays an important part in blocking the "cancer immunity cycle" by binding to and stimulating PD-1 and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008; Herbst et al. 2014). B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation, and secretion of cytotoxic mediators, and restricts tumor cell killing, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011; Herbst et al. 2014). The

PD-1/PD-L1 pathway has been implicated in tumors evading immune surveillance. Blockage of the PD-1/PD-L1 interaction enables the rapid restoration of the effector function of preexisting anti-cancer T cells (Chen and Mellman 2013; Saha and Nanda, 2016). Blocking PD-L1 should therefore enhance anti-cancer immunity (Herbst et al. 2014).

Based on available clinical trial evidence, blockade of the PD-1/PD-L1 axis with atezolizumab (Emens et al. 2021; Adams et al. 2018; Schmid et al. 2018, 2020), pembrolizumab (Adams et al. 2019a, 2019b; Cortes et al. 2020), or avelumab (Dirix et al. 2018) is a viable treatment strategy in patients with advanced TNBC.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 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 crystallisable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab (Tecentriq) is approved in several countries around the world for the treatment of urothelial carcinoma, metastatic NSCLC, SCLC, TNBC, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

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

1.2.1 Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were, thus, undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the

appropriate starting dose in humans. Given the similar binding of atezolizumab with cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

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

1.2.2 Clinical Studies in Patients with TNBC

Atezolizumab is being investigated in multiple Phase I, II, and III clinical studies, both as monotherapy and in combination with several anti-cancer therapies against solid tumors and hematologic malignancies (see the Atezolizumab Investigator's Brochure for study descriptions).

Anti-tumor activity, as determined by RECIST v1.1 response, has been observed across multiple advanced tumor types for both atezolizumab monotherapy as well as in combination with bevacizumab and/or chemotherapy; refer to the Atezolizumab Investigator's Brochure for details. In patients with mTNBC, atezolizumab has shown activity when given as monotherapy (Emens et al. 2015; Schmid et al. 2017) and in combination with nab-paclitaxel (Adams et al. 2016; Schmid et al. 2018, 2019; Emens et al. 2021). Combining atezolizumab with chemotherapy is hypothesized to enhance tumor-specific T-cell immunity by exposing the immune system to high levels of chemotherapy-induced tumor antigens and modulating T-cell and natural killer–cell functions (Adams et al. 2016).

1.2.3 Atezolizumab Combined with Chemotherapy in Patients with TNBC

1.2.3.1 Study GP28328, Subpopulation with mTNBC

Building on the promising results of atezolizumab as a single agent, an open-label Phase Ib trial (GP28328; clinicaltrials.gov identifier: NCT01633970) was initiated to evaluate atezolizumab in combination with chemotherapy and/or bevacizumab in locally advanced or metastatic solid tumors. One of the arms (Arm F; n=33) evaluated 4-week cycles consisting of atezolizumab 800 mg every 2 weeks (Q2W; Days 1 and 15) in combination with nab-paclitaxel 125 mg/m^2 Q1W (Days 1, 8, and 15) in patients with mTNBC, treated with ≤2 prior lines of therapy for metastatic disease. After nab-paclitaxel discontinuation, maintenance atezolizumab was allowed until loss of clinical benefit. The primary endpoints were safety and tolerability; secondary endpoints included measures of clinical activity, and biomarker analyses. Results after a median follow-up of 24.4 months (95% CI: 22.1 to 28.8 months) were recently reported (Adams

et al. 2018). The objective response rate (ORR) was 39.4% (95% CI: 22.9% to 57.9%), and the median duration of response (DoR) was 9.1 months (95% CI: 2.0 to 20.9 months). The disease control rate (DCR) was 51.5% (95% CI: 33.5% to 69.2%). Median progression-free survival (PFS) and overall survival (OS) were 5.5 months (95% CI: 5.1 to 7.7 months) and 14.7 months (95% CI: 10.1 to not estimable), respectively. Concurrent nab-paclitaxel had no significant effect on biomarkers of the tumor immune microenvironment (PD-L1, TILs, CD8) or on atezolizumab systemic immune activation (expansion of proliferating $CD8^+$ T cells, increase of CXCL10 chemokine) (Adams et al. 2018).

As of 23 April 2018, all 33 safety-evaluable patients (100% with) mTNBC experienced at least one adverse event (AE), 28 patients (84.8%) experienced a Grade 3 or 4 AE, no patient experienced a Grade 5 AE, 18 patients (54.5%) experienced an SAE, and 3 (9.1%) experienced an AE leading to discontinuation of atezolizumab. Refer to the Atezolizumab Investigator's Brochure for details. Treatment-related AEs, Grade 3 and 4 AEs, and Grade 3 and 4 AEs of special interest (AESI) occurred in 100%, 73%, and 21% of patients, respectively. The most common treatment-related AEs were neutropenia/decreased neutrophil count (70%), diarrhea (39%), peripheral neuropathy (30%), anemia (24%), thrombocytopenia/decreased platelet count (15%), myalgia (15%), and bone pain (12%) (Adams et al. 2018).

1.2.3.2 Study WO29522 (IMpassion130)

Based on the tolerability and promising activity of atezolizumab in mTNBC, the combination of atezolizumab and nab-paclitaxel has been evaluated in a global, randomized, placebo-controlled Phase III study (WO29522/IMpassion130; ClinicalTrials.gov identifier: NCT02425891) in previously untreated unresectable locally advanced or metastatic TNBC patients (n = 902). Eligible patients were randomized in a 1:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Prespecified co-primary efficacy endpoints included investigator-assessed PFS by RECIST v1.1 (in the intent-to-treat [ITT] and PD-L1–positive populations), and OS (in the ITT and PD-L1–positive populations) (Schmid et al. 2018, 2019, 2020).

A total of 902 patients were randomized in the study; 451 in each group. In the atezolizumab plus nab-paclitaxel and placebo plus nab-paclitaxel groups, respectively, median age was 55 and 56 years, respectively; 57% and 60%, respectively had Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, and 63% each received prior (neo)adjuvant treatment. The PD-L1–-positive population included 369 patients (185 and 184 patients in the two groups, respectively). Analysis of the co-primary efficacy endpoints (final for PFS, and first interim for OS), completed after 736 PFS events (representing 81.6% of patients) and 389 deaths (43.1%) had occurred in the ITT population (median follow-up of 12.9 months), showed that treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel resulted in a statistically

significant reduction in the risk of disease worsening or death in the ITT population (median PFS: 7.2 vs. 5.5 months, respectively; HR: 0.80, 95% CI: 0.69 to 0.92; p=0.002). In the PD-L1–positive population, median PFS was 7.5 versus 5.0 months in the two groups, respectively (HR: 0.62, 95% CI: 0.49 to 0.78, p≤0.001). At this first interim analysis of OS, there was a trend for prolonged OS in the ITT population (median OS: 21.3 vs. 17.6 months, respectively; HR: 0.84; 95% CI: 0.69 to –1.02; p=0.08), with a clinically meaningful 9.5-month OS improvement in the PD-L1–positive subpopulation (median OS: 25.0 vs. 15.5 months, respectively; HR: 0.62, 95% CI: 0.45 to 0.86). Due to the hierarchical statistical design, OS results were not formally tested in the PD-L1–positive subpopulation. In the ITT population, investigator-assessed ORR was 56% in the atezolizumab plus nab-paclitaxel group compared to 46% in the placebo plus nab-paclitaxel group (treatment-difference 10%, p=0.002). In the PD-L1–positive subpopulation, ORRs were 59% versus 43% in the two groups, respectively (treatment difference: 16%; p=0.002). Median DoR was 7.4 months versus 5.6 months in the two groups, respectively in the ITT population, and 8.5 months versus 5.5 months, respectively in the PD-L1-positive subpopulation (Schmid et al. 2018; WO29522 Primary Clinical Study Report, Report No. 1085705; Roche data on file).

A pre-planned second interim OS analysis for IMpassion130 was performed based on a clinical cutoff date (CCOD) of 2 January 2019, after 534 patients (59.2%) had died in the ITT population (median survival follow-up of 18.0 months). Consistent with the OS results at the first interim analysis, the co-primary endpoint of OS at the second interim analysis was not significant in the ITT population as the prespecified boundary (HR: ≤0.818; available $\alpha=0.021$) was not crossed (stratified HR: 0.86; 95% CI: 0.72 to 1.02, p=0.0777). Due to the prespecified Statistical Analysis Plan (SAP) entailing hierarchical testing for OS first in the ITT and then in the PD-L1–positive population, the difference between the treatment arms for OS in the PD-L1–positive population was not formally tested. However, a clinically meaningful improvement in OS continued to be observed in the PD-L1–positive population, with median OS of 25.0 months vs. 18.0 months in the atezolizumab plus nab-paclitaxel compared to the placebo plus nab-paclitaxel group, respectively (stratified HR: 0.71; 95% CI: 0.54 to 0.93) (Schmid et al. 2020; WO29522 Update Clinical Study Report, Report No. 1092074; Roche data on file). At the final OS analysis, completed after 666 patients (73.8%) had died in the ITT population (median survival follow-up of 18.8 months), median OS in the atezolizumab plus nab-paclitaxel group compared with the placebo plus nab-paclitaxel group was 21.0 months relative to 18.7 months, respectively, in the ITT population (stratified OS HR: 0.87, 95% CI:0.75 to 1.02; p=0.077), and 25.4 months vs. 17.9 months, respectively, in the PD-L1–positive population (stratified OS HR: 0.67, 95% CI: 0.53 to 0.86; not formally tested due to the prespecified testing hierarchy) (Emens et al. 2020; WO29522 Update Clinical Study Report, Report No. 1100481; Roche data on file).

As of the second interim OS analysis, consistent with results of the first interim OS analysis, a statistically significant improvement in investigator-assessed PFS was

demonstrated with atezolizumab plus nap-paclitaxel relative to placebo plus nab-paclitaxel in both the ITT population (stratified HR: 0.80; 95% CI: 0.69 to 0.92; p=0.0021) and the PD-L1–positive population (stratified HR:0.63, 95% CI: 0.50 to 0.80; p=< 0.0001). While the PFS analysis was already final at the time of the first interim OS analysis, the updated PFS analysis results presented as of the second interim OS analysis confirm the long-term benefit in the PD-L1–positive population and remain consistent, statistically significant and clinically meaningful (Atezolizumab Investigator's Brochure).

As of the latest CCOD of 14 April 2020, safety data were available for 890 patients with metastatic TNBC in the safety-evaluable population (460 in the atezolizumab plus nab-paclitaxel group and 430 patients in the placebo plus nab-paclitaxel group). AEs occurred in 99% relative to 98% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups and Grade 3–4 AEs occurred 51% compared with 43% of patients in the two groups. AEs (all grades) that occurred at a ≥5% higher frequency in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel group included nausea (47% vs. 38%, respectively), cough (27% vs. 19%), neutropenia (22% vs. 15%, respectively), pyrexia (20% vs. 11%, respectively), pruritus (16% vs. 11%), dizziness (15% vs. 10%,), hypothyroidism (14% vs. 4%,), and stomatitis (11% vs. 5%,). The only Grade 3–4 AEs occurring in >5% of patients were neutropenia reported in 8.5% relative to 8.1% of patients in the atezolizumab plus nab-paclitaxel group compared to placebo plus nab-paclitaxel group), and peripheral neuropathy (reported in 5.7% vs. 2.8% of patients in the two groups, respectively) (WO29522 Update Clinical Study Report, Report No. 1100481; Roche data on file).

Serious adverse events (SAEs) occurred in 23.9% compared with 18.6% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups, respectively, and fatal AEs occurred in 1.3% vs 0.7% of patients in the two groups. Two of the six fatal AEs in the atezolizumab plus nab-paclitaxel group (autoimmune hepatitis [considered related to blinded study drug/atezolizumab], and septic shock [considered related to nab-paclitaxel], and one of three fatal AEs in the placebo plus nab-paclitaxel group (hepatic failure [considered related to blinded study drug/placebo and nab-paclitaxel]) were assessed by the investigator as treatment related. One patient in each group experienced a Grade 5 AESI (autoimmune hepatitis in the atezolizumab plus nab-paclitaxel group and hepatic failure in the placebo plus nab-paclitaxel group) (WO29522 Update Clinical Study Report, Report Number 1100481; Roche data on file).

AESI occurred in 59% and 42% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel group, respectively. Most AESI (≥□86% in each group) were assessed as Grade 1 or 2 in severity. Grade 3–4 AESI occurred in 8.5% and 4.7% of patients in the two groups, respectively. Sixteen percent and 7% of patients in the two groups, respectively, received systemic corticosteroids within 30 days of AESI onset. The only between-group differences in the frequency of any grade AESI were for immune-mediated rash (36% vs. 26%, respectively), immune-mediated

hypothyroidism (18% vs. 4%), immune-mediated hyperthyroidism (5% vs 1%), and immune-mediated pneumonitis (4% vs. <1%). Overall, combination treatment with atezolizumab plus nab-paclitaxel was well tolerated in this study, with a safety profile consistent with that of each agent. No cumulative toxicities or new or late-onset safety signals were seen with longer follow-up (WO29522 Update Clinical Study Report, Report Number 1100481; Roche data on file).

1.2.3.3 Study MO39196 (IMpassion131)

Study MO39196 (IMpassion131; ClinicalTrials.gov identifier: NCT03125902) is an ongoing global Phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and pharmacokinetics of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with unresectable locally advanced or metastatic, centrally confirmed TNBC who have not received prior systemic therapy for these conditions. Eligible patients were randomized in a 2:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus paclitaxel (90 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. The primary endpoint of investigator-assessed PFS by RECIST v1.1 was tested hierarchically in the following prespecified fixed order: (1) In the subpopulation with PD-L1-positive tumor status (IC ≥1%) (2) In the ITT population: safety endpoints include the incidence of AEs, changes in vital signs, physical examination findings, and clinical laboratory tests. Immunogenicity (the incidence of anti-drug antibodies [ADAs] during the study relative to the prevalence of ADAs at baseline) will also be evaluated.

Of the 651 randomized patients, 292 patients (45%) had PD-L1–positive metastatic TNBC. Primary analyses of PFS were completed after 179 PFS events (representing 61.3% of patients) and 438 PFS events (67.3% of patients) had occurred in the PD-L1–positive and ITT populations, respectively. The results showed no significant improvement in the atezolizumab plus paclitaxel compared to the placebo plus paclitaxel group in either the PD-L1–positive subset (median PFS: 6.0 vs 5.7 months, respectively; HR: 0.82; 95% CI: 0.60 to 1.12; p=0.20) or in the ITT population (median PFS: 5.7 months vs. 5.6 months, respectively). Similarly, analysis of OS (a secondary endpoint), completed after 120 patients (41.1%) and 304 patients (46.7%) had died in the PD-L1–positive and ITT populations, respectively, showed no significant survival benefit in either population (Miles et al. 2020).

Overall, the safety profile was consistent with the known risks of each study drug. Two percent of patients in each group experienced a Grade 5 AE. The percentages of patients experiencing Grade 3/4 AEs were similar among patients treated with atezolizumab and paclitaxel compared to placebo and paclitaxel (49% vs. 43%, respectively) (Miles et al. 2020).

1.2.3.4 Immune-Mediated Adverse Events

The safety data presented in this section is based on pooled data from 3178 patients with multiple tumor types and supporting data from the estimated cumulative exposure in

>23,000 patients across all clinical trials. The overall immune-mediated adverse drug reaction (ADR) rate for atezolizumab monotherapy is 12.7%, the majority of which were Grade 1–2 immune-mediated ADRs.

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. Important identified risks associated with atezolizumab include the occurrence of the following immune-mediated AEs (listed with total frequencies of these events in pooled clinical trials of atezolizumab): immune-mediated pneumonitis (2.7% [87/3178]); immune-mediated hepatitis (2.0% [62/3178]); immune-mediated colitis (1.1% [34/3178]); immune-mediated pancreatitis (0.6% [18/3178]); immune-mediated endocrinopathies, including diabetes mellitus (0.3% [11/3178]), hypothyroidism (5.2% [164/3178]), hyperthyroidism (0.9% [30/3178]), and adrenal insufficiency (0.3% [11/3178]); immune-mediated hypophysitis (<0.1% [2/3178]); immune-mediated neuropathies, including myasthenic syndrome/myasthenia gravis (<0.1%), and Guillain-Barré syndrome (0.2% [5/3178]); immune-mediated facial paresis (<0.1%); immune-mediated myelitis (<0.1%); immune-mediated meningoencephalitis (0.4% [14/3178]); immune-mediated myocarditis (<0.1%), immune-mediated pericardial disorders (1.4% [45/3178]), immune-mediated nephritis (<0.1% [3/3178], including one case of Henoch-Schoenlein purpura nephritis), immune-mediated myositis (0.4% [13/3178]), *and immune-mediated severe cutaneous adverse reaction (0.7% [22/3178]*; in addition, there have been 34 cases of infusion-related reactions (1.1%) (see Section 6 of Atezolizumab Investigator's Brochure). Overall, the nature and frequency of immune-mediated AEs have been consistent across multiple tumor types in clinical studies of atezolizumab.

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

Treatment-emergent (treatment-induced plus treatment-enhanced) anti-drug antibodies (ADAs) have been observed in the clinical trials of atezolizumab, at doses of 10 mg/kg and above. In the monotherapy all patient population, the post-baseline incidence of treatment-emergent atezolizumab ADAs (treatment induced and enhanced) was 35.2% (*1219/3460*). In the monotherapy all patient population, the incidence of all grade AEs, Grade 5 AEs, AEs leading to treatment withdrawal, AEs leading to dose interruption and AESI was similar irrespective of post-baseline ADAs status (negative or positive). The incidence of SAEs and Grade 3–4 AEs was increased in ADA-positive compared with ADA-negative patients (SAEs: *39.4*% vs 33.0%, respectively; Grade 3–4 AEs 45.9% vs *39.1*%, respectively); however, none of these events were driven by any specific System Organ Class or individual AE. In the monotherapy all-patient population, the incidence of hypersensitivity events and infusion-related reactions was low and consistent between ADA-positive and ADA-negative patients.

In the IMpassion130 study, the incidence of treatment-emergent ADAs among patients receiving atezolizumab plus nab-paclitaxel was 13.1% and 11.8% in the ITT and PD-L1–positive populations, respectively. ADA positivity had no clinically relevant effect on pharmacokinetics, although, on average, C_{min} at steady state was approximately 25% lower in ADA-positive patients compared with ADA-negative patients. The overall safety profile was generally concordant between ADA-positive and ADA-negative patients based on the incidence of related AEs (93.0% vs. 97.9%, respectively), related Grade 3–4 AEs (40.4% vs. 40.6%, respectively), SAEs (28.1% vs. 21.5%, respectively), AEs leading to study treatment discontinuation (17.5% vs. 15.9%, respectively), and AESI (52.6% vs. 58.6%, respectively) (WO29522 Primary Clinical Study Report, Report No. 1085705; Roche data on file).

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The primary analysis of the IMpassion130 (WO29522) study, a global, randomized, placebo-controlled Phase III study designed to evaluate the combination of atezolizumab plus nab-paclitaxel in patients with unresectable locally advanced or metastatic TNBC who have not received prior chemotherapy for their disease showed encouraging results in the PD-L1–positive subpopulation; refer to Section 1.2.3.2 for details. Exploratory efficacy analyses from IMpassion130 indicated that PD-L1 expression on immune cells (ICs) is the most robust predictive biomarker for selecting untreated mTNBC patients who benefit from atezolizumab plus nab-paclitaxel. Intratumoral CD8 was well correlated with PD-L1-positivity, and was consequently predictive of atezolizumab plus nab-paclitaxel efficacy for PFS and OS (Emens et al. 2021).

The MO39874 study aims to build on the data from IMpassion130 (WO29522) study with a primary objective to evaluate the safety of atezolizumab in combination with nab-paclitaxel in a broader population of patients with advanced TNBC.

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

1.3.1 COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more 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 appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). 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.

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

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy 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 immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4).

The solvents used to enhance the solubility of taxanes have been associated with allergic reactions and peripheral neuropathy (ten Tije et al. 2003). However, nab-paclitaxel is an albumin-bound formulation of paclitaxel that was developed to avoid the toxicities associated with the vehicles that are necessary for parenteral administration of solvent-based paclitaxel (polyethylated castor oil and polysorbate 80), and therefore can be administered without corticosteroid or antihistamine premedication.

This trial will enroll patients with unresectable locally advanced or mTNBC. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. Results of a recently reported safety study (MO29983, SAUL study; n=1004) confirmed the tolerability of atezolizumab in patients with pretreated locally advanced or metastatic urinary tract carcinoma and poor prognosis, including in patients with autoimmune disease, concomitant corticosteroid treatment, central nervous system (CNS) metastases, renal impairment, and ECOG Performance Status of 2 (Sternberg et al. 2019).

The benefit–risk ratio for atezolizumab in combination with nab-paclitaxel is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

The primary aim of this study is to evaluate the safety of atezolizumab plus nab-paclitaxel in patients with PD-L1–positive unresectable locally advanced or metastatic triple-negative adenocarcinoma of the breast (TNBC) who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC. The study will also evaluate treatment efficacy. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Safety Objective	**Primary Safety Endpoints**
• To evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1–positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• Incidence of treatment-emergent Grade ≥3 AEs • Incidence of treatment-emergent Grade ≥2 imAEs [a]
Secondary Safety Objective	**Secondary Safety Endpoints**
• To further evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• Incidence of all treatment-emergent AEs • Incidence of treatment-emergent SAEs
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To evaluate the effect of atezolizumab plus nab-paclitaxel on key survival outcomes in patients with unresectable locally advanced or metastatic PD-L1–positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• OS, defined as the time from initiation of study treatment to death from any cause (analyzed in the ITT population, and in the subset of patients with centrally confirmed PD-L1–positive tumor status) • PFS, defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first (analyzed in the ITT population, and in the subset of patients with centrally confirmed PD-L1–positive tumor status). PFS will be assessed by the investigator according to RECIST v1.1

AE = adverse event; CNS = central nervous system; CR = complete response; DCR = disease control rate; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; ER/PgR = estrogen receptor/progesterone receptor; imAE = immune-mediated adverse event; ORR = objective response rate; OS=overall survival; PD-1 = programmed cell death–protein 1; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TNBC = triple-negative breast cancer; v = version

[a] Immune-mediated adverse events (imAEs) are events that resemble autoimmune diseases and are known side effects of immune checkpoint inhibitors, including atezolizumab; refer to Section 1.2.3.4 for details.

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoint(s)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the anti-tumor effects of atezolizumab plus nab-paclitaxel, as measured by investigator-determined ORR, DCR, and DoR according to RECIST v1.1 in patients with unresectable locally advanced or metastatic PD-L1–positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	• ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved CR or PR as determined by the investigator using RECIST v1.1. • DCR, defined as the sum of the CR, PR and SD rates • DoR, defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first In addition, [redacted]
• To further describe the safety and efficacy of atezolizumab plus nab-paclitaxel in subgroups of patients with unresectable locally advanced or metastatic PD-L1-positive TNBC who have not received prior systemic therapy for unresectable locally advanced or metastatic TNBC	Selected safety and efficacy endpoints will be described by subgroups determined at baseline according to the following parameters: – Presence of CNS metastases (yes vs. no) – ECOG performance status (0 or 1 vs. 2) – Prior anticancer treatment (yes vs. no) – Prior anticancer treatment with PD-1/PD-L1 (yes vs. no) – Prior use of taxane vs non-taxane therapy in (neo)adjuvant settings
Exploratory Biomarker Objective	**Exploratory Endpoints**
• To evaluate the inter-observer concordance in PD-L1 status determined by local vs central laboratory testing, using the VENTANA PD-L1 SP142 Assay	• PD-L1 status determined by local vs central laboratory testing, using the VENTANA PD-L1 SP142 Assay

AE = adverse event; CNS = central nervous system; CR = complete response; DCR = disease control rate; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; ER/PgR = estrogen receptor/progesterone receptor; imAE = immune-mediated adverse event; ORR = objective response rate; OS=overall survival; PD-1 = programmed cell death–protein 1; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TNBC = triple-negative breast cancer; v = version

[a] Immune-mediated adverse events (imAEs) are events that resemble autoimmune diseases and are known side effects of immune checkpoint inhibitors, including atezolizumab; refer to Section 1.2.3.4 for details.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study MO39874 is an open-label, Phase IIIb, single arm, global study conducted in patients with unresectable locally advanced or metastatic PD-L1–positive TNBC who have not received chemotherapy for their unresectable locally advanced or metastatic disease. TNBC is defined as HER2, ER and PgR-negative disease, determined in accordance with the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Hammond et al. 2010; Wolff et al. 2018; Allison et al. 2020). Confirmation of TNBC status will be completed locally and PD-L1 testing (using the VENTANA® PD-L1 SP142 assay) will be completed locally and centrally. Patients who received prior treatment for early-stage disease are permitted in this study, provided they meet the treatment-free interval (TFI) requirements detailed in the inclusion criteria.

Patients will be assessed for eligibility during the 28-day screening period prior to enrolment. Enrolment is defined as the date and time when the patient's eligibility for the study is confirmed and registration is completed in the interactive voice/web response system (IxRS). Enrolled patients will begin treatment with atezolizumab 840 mg administered via intravenous (IV) infusion on Days 1 and 15 of every 28-day cycle in combination with nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle.

In the absence of disease progression (PD) or unacceptable toxicity, study treatment will continue until the end of the study (EOS). Atezolizumab or nab-paclitaxel may be discontinued for toxicity and re-started independently of one another in the absence of disease progression.

Tumor assessments will be performed [redacted] thereafter until PD per RECIST v1.1 or death, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Tumor assessments will be performed according to the specified schedule regardless of treatment delays.

Treatment will be discontinued upon radiographic PD per RECIST v1.1. Consistent with RECIST v1.1, in case of equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Follow-up for new anti-cancer therapy and survival will continue for up to [redacted] after the last patient is enrolled in the study.

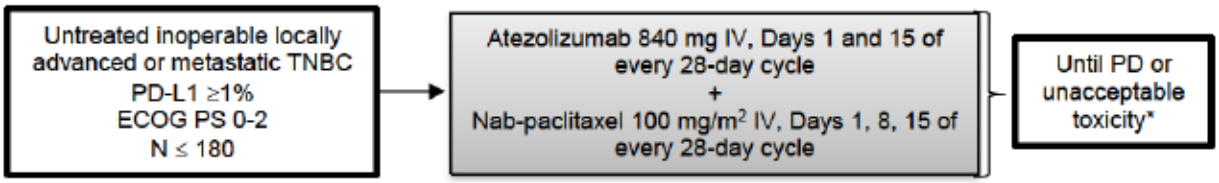
Safety assessments will include regular evaluation of AEs and conduct of physical examinations, vital signs, and clinical laboratory tests (haematology, blood chemistry, thyroid hormones). AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (v5.0).

After initiation of study treatment, all adverse events (regardless of relationship to study drug) 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. SAEs and AESI 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 the end of the reporting period for SAEs and AESI (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.

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter.

The schedule of study activities is provided in Appendix 1. A study design schema is presented in Figure 1.

Figure 1 Study Schema



Abbreviations: ECOG = Eastern Cooperative Oncology Group IV = intravenous(ly); N = number of patients; PD = disease progression; PD-L1 = programmed death-ligand 1; PS = Performance Status; TNBC = triple-negative breast cancer

* Additional reasons for study treatment discontinuation may include loss of clinical benefit as determined by the investigator, or patient decision.

3.1.2 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will be established for the study to review all AEs, SAEs and AESI and cumulative safety data. Details of the composition of the IMC, the safety review plan and procedures for data review will be provided in the IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study (EOS) is defined as the last patient's last visit (LPLV), and will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or

have been followed for [redacted] since the last study patient was enrolled, whichever occurs first.

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

The total length of the study, from screening of the first patent to the end of the study, is expected to be approximately 4.5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for the Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 840 mg every two weeks (Q2W; 840 mg on Days 1 and 15 of each 28-day cycle), which is the approved dosing regimen for TNBC (refer to the TECENTRIQ™ prescribing information). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg every 3 weeks (Q3W). Of note, the exact equivalent dose is 800 mg; however, because atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL, and in the interest of simplifying administration, the exact dose used in this study will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single syringe. The 840-mg dose is not expected to result in meaningfully different exposure compared with the 800-mg dose.

In the Phase Ia study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any of the doses tested (from 0.1 to 20 mg/kg). ADAs to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but not for patients treated at 10, 15, and 20 mg/kg, including the approved dose of 1200 mg. To date, no relationship has been observed between the development of measurable ADAs and safety or efficacy.

Combination regimens including atezolizumab 840 mg Q2W have been evaluated in several global Phase III clinical trials involving patients with untreated, unresectable locally advanced or metastatic TNBC. Taxane regimens used in combination with atezolizumab included nab-paclitaxel 100 mg/m^2 IV infusions on Days 1, 8, and 15 of each 28-day cycle in the IMpassion 130 study (Schmid et al. 2018), and paclitaxel 90 mg/m^2 IV infusions on Days 1, 8, and 15 of every 28-day cycle in the IMpassion131 study.

3.3.2 Rationale for the Patient Population

This study will enroll patients with unresectable locally advanced or metastatic TNBC who are positive for PD-L1 (defined as PD-L1 expression ≥1% on tumor-infiltrating ICs as percentage per tumor area), have not received prior systemic therapy for their unresectable locally advanced or mBC, and are suitable for atezolizumab and taxane therapy. Patients will be either newly diagnosed or have disease progression after completing treatment for early breast cancer, in which case, a minimum treatment-free

interval (TFI) will be observed (see below). Locally advanced disease must not be amenable to resection with curative intent.

Atezolizumab showed promising anti-tumor activity, as determined by RECIST v1.1 response, across multiple advanced tumor types, including TNBC. In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2019), and most notably in combination with nab-paclitaxel (Adams et al. 2018; Schmid et al. 2018, 2019).

The rationale for enrolling patients with PD-L1–positive tumor status is based on the results of the primary analysis of PFS in the global, randomized, double-blind, Phase III IMpassion130 study, and specifically on the result in the PD-L1–positive subpopulation (Schmid et al. 2018, 2019), and aligned with the currently approved labels for atezolizumab. Analysis of the co-primary efficacy endpoints (final for PFS, and 1st interim for OS) in the PD-L1–positive population showed that after a median follow-up of 12.9 months, treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel resulted in significantly prolonged PFS (median PFS: 7.5 vs. 5.0 months, respectively; HR: 0.62; , 95% CI: 0.49 to 0.78, $p \leq 0.0001$), and longer OS (median OS: 25.0 vs 15.5 months, respectively; HR: 0.62, 95% CI: 0.45 to 0.86); due to the prespecified hierarchical testing for OS first in the ITT and then in the PD-L1–positive population, the difference between the treatment arms for OS in the PD-L1–positive population was not formally tested.

In addition, in the PD-L1–positive subpopulation, treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel was associated with longer investigator-assessed ORR (59% vs 43%, respectively; (treatment difference 16%; p=0.0016), and median DoR (8.5 months vs 5.5 months, respectively) (Schmid et al. 2018, 2019). The survival benefit in the PD-L1-population was maintained at the second interim analysis of OS (median OS of 25.0 months vs 18.0 months in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups, respectively; stratified HR: 0.71; 95% CI: 0.54 to 0.93) and at the final analysis of OS (median OS of 25.4 months vs. 17.9 months in the two groups, respectively; stratified OS HR: 0.67; 95% CI: 0.53 to 0.86; not formally tested due to the prespecified testing hierarchy); refer to Section 1.2.3.1 for further details.

In addition, to complete the study under conditions reflective of real-life setting, the eligibility criteria have been adjusted to include patients with the following conditions/status at baseline:

- PD-L1–positive tumor status will be confirmed locally and centrally, using the VENTANA PD-L1 SP142 assay. The Ventana® SP142 assay for the assessment of the PD-L1 protein in tumor cells and tumor-infiltrating ICs in the FFPE tissues received indication-specific approval from the U.S. Food and Drug Administration (FDA) in March 2019 (FDA 2019).

- Patients who received prior treatment in the (neo)adjuvant setting are permitted on study provided they meet the minimum TFIs requirements prior to the first dose of study treatment: 12 months for taxane-based regimens and for PD-1/PD-L1–based regimens, and 6 months for other chemotherapy regimens (including capecitabine)
- ECOG Performance Status 0 to 2 (see Appendix 5)
- Certain pre-specified autoimmune diseases, if stable and controlled
- Patients with asymptomatic central nervous system (CNS) metastases (excluding metastases to the midbrain, pons, medulla, or cerebellum), are permitted if stable, and suitable for study treatment in the investigator's judgement.

Patients with TNBC (compared to other subtypes) are at higher risk of brain metastases (Darlix et al. 2018), and have the shortest survival following diagnosis of brain metastases (4.6 months compared to 11.6 months in patients with HER2-positive tumors) (Witzel et al. 2018). Brain metastases are detected more commonly in patients with TNBC compared with other subtypes at initial diagnosis (0.7% vs 0.3%–0.4% for all BC types) (Martin et al. 2017; Xiao et al. 2018; Ascha et al. 2019), and ultimately about half of the patients with TNBC develop brain metastases (O'Sullivan et al. 2017). Prognosis in these patients is particularly poor, as current therapeutic options are considered palliative (Shah et al. 2018). There are also very limited clinical trial data in this population. As described in Section 1.3, results of the recently reported SAUL study (MO29983; n = 1004) confirmed the tolerability of atezolizumab in cancer patients with poor prognosis, including in patients with CNS metastases (Sternberg et al. 2019).

Patients with positive human immunodeficiency virus (HIV) test at screening may be allowed, provided that they are stable on anti-retroviral therapy, have a CD4 count >200/mL, and have an undetectable viral load.

In addition, patients will be allowed under certain condition described in the protocol to receive steroid treatments (prednisone at a dose of ≤ 20 mg/day, or equivalent).

3.3.3 Rationale for the Open-Label Design

An open-label study design was chosen for this trial for a number of reasons. MO39874 is a safety study planned to be completed under conditions closely resembling real-life setting, and as such, not suitable for a double-blind, randomized design. In addition, given that the combination of atezolizumab and nab-paclitaxel has been demonstrated to provide PFS and OS benefits in patients with PD-L1–positive advanced or mTNBC (Schmid et al. 2018), prolonged administration of placebo in this population during a blinded study would be considered unethical , as well as pose a significant burden to patients.

3.3.4 Rationale for Concomitant Taxane Treatment

The taxane class of cytotoxic agents (paclitaxel, docetaxel, nab-paclitaxel) have significant anti-tumor activity in breast cancer. Despite the expansion of the therapeutic

landscape for mBC over the last three decades, including the increasing availability of targeted therapies for various BC subtypes, taxane-based regimens remain standard of care in first-line therapy for patients with mBC, including TNBC (Cardoso et al. 2012; Greene and Hennessy 2015; Hernandez-Aya and Ma 2016; Fukada et al. 2016).

Several studies and meta-analyses support the benefit of taxanes on clinical outcomes in mBC (Piccart-Gebhart et al. 2008; Qi et al. 2013; Ghersi et al. 2015), including their favorable efficacy compared to the anthracycline regimens (Ghersi et al. 2015).

Nab-paclitaxel is approved for the treatment of recurrent and metastatic BC in many countries. As described in Section 1.2 above, atezolizumab in combination with nab-paclitaxel has shown promising anti-tumor activity in patients with mTNBC (Adams et al. 2018a, 2018b; 2020), particularly in patients with PD-L1–positive tumor status (Schmid et al. 2018, 2020). In the IMpassion130 study (Schmid et al. 2018, 2020), treatment with atezolizumab (840 mg IV on Days 1 and 15 of every 28-day cycle) plus nab-paclitaxel (100 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle) compared to a matching placebo plus nab-paclitaxel regimen was associated with significantly longer PFS, OS, investigator-assessed objective response rate (ORR), and DoR in the PD-L1–positive subpopulation; refer to Section 1.2.3.2 for details.

Taken together, available data support the selected regimen for nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) used in combination with atezolizumab in the current study.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will include patients with unresectable locally advanced or metastatic TNBC with PD-L1–positive tumor status (defined as PD-L1 expression ≥1% on tumor-infiltrating ICs as percentage per tumor area), who have not received prior systemic therapy for their unresectable locally advanced or mBC, and are suitable for atezolizumab and taxane therapy. PD-L1–positive status will be determined locally and centrally using VENTANA PD-L1 SP142 assay. Negative ER/PgR status (defined as <1% of tumor cell nuclei being immunoreactive by IHC) must be confirmed in at least one tumor sample (primary and/or metastatic) using a validated test. Locally advanced disease must not be amenable to resection with curative intent. For patients who received prior chemotherapy in the neoadjuvant/adjuvant setting, the following TFIs must be observed prior to the first dose of study treatment (Cycle 1, Day 1): 12 months for taxane-based regimens (irrespective of capecitabine) and PD-1/PD-L1–based regimens, and 6 months for other chemotherapy regimens (including capecitabine). Patients with *de novo* mTNBC may also be enrolled. Patients must comply with all eligibility criteria to be enrolled.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Have provided written informed consent.
- Female or male ≥18 years of age.
- Ability to comply with the study protocol, in the investigator's judgment.
- Patients with unresectable locally advanced or metastatic, histologically documented TNBC (negative for HER2 and ER and PgR)

  HER2 negativity is defined as either of the following: IHC 0, IHC 1+ or IHC2+/in situ hybridization (ISH)-negative, as per the current ASCO-CAP guideline (Wolff et al. 2018).

  ER/PgR negativity (defined as <1% of tumor cells expressing ER and PgR hormonal receptors) must be confirmed in at least one tumor sample (primary and/or metastatic) using a validated IHC test as per the current ASCO-CAP guideline (Hammond et al. 2010; Allison et al. 2020).
- Patient with at least one specimen positive for PD-L1 status as determined by VENTANA PD-L1 SP142 IHC assay.

  Specimens with PD-L1 expression on tumor-infiltrating ICs covering ≥1% of tumor area would be PD-L1 positive, whereas PD-L1 expression on ICs covering <1% of tumor area would be PD-L1 negative.

  If multiple tumor specimens are available, patients may be eligible if at least one specimen is evaluable for PD-L1 testing and shows PD-L1 expression on ≥1% ICs.

  Acceptable samples include core needle biopsies for deep tumor tissue (more than one core if clinically feasible) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

  Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

  Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  In case of previous hormonal-receptor–positive breast cancer (HR^+BC), a biopsy from metastatic site (or unresectable locally advanced disease) showing TNBC is mandatory. PD-L1 positivity must also be confirmed in a TNBC sample (regardless of site).
- No prior chemotherapy, experimental or targeted systemic therapy for unresectable locally advanced or metastatic TNBC

  Radiation therapy for metastatic disease is permitted. There is no required minimum treatment-free period for radiation therapy. Patients should have recovered from the effects of radiation.

  Prior pharmacological treatment in the neoadjuvant or adjuvant setting is allowed, as long as the following TFI) are observed prior to the first dose of study treatment (Cycle 1, Day 1):

i. Prior taxane-based chemotherapy: ≥ 12 months

ii. Prior PD-1/PD-L1-based regimen: ≥ 12 months

iii. Any other regimen (including capecitabine or non-taxane chemotherapy): ≥6 months

iv. Adjuvant hormonal therapy: 2 weeks

Chinese traditional medicines with an approved indication for cancer treatment are permitted as long as the last administration occurred at least 2 weeks prior to enrolment.

Patients with *de novo* mTNBC may also be enrolled.

- ECOG Performance Status of 0, 1 or 2
- Life expectancy ≥12 weeks.
- Measurable disease, as defined by RECIST v1.1.

  Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.
- Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the initiation of study treatment (Cycle 1, Day 1):

– Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1500 cells/μL) (without granulocyte colony-stimulating factor (G-CSF) support within 2 weeks prior to Cycle 1, Day 1; G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1).

– Lymphocyte count $\geq 0.5 \times 10^9$/L (500 cells/μL), except in human immunodeficiency virus (HIV) carriers, who need to have a lymphocyte count $\geq 1.2 \times 10^9$/L (1200 cells/μL)

– Platelet count $\geq 100 \times 10^9$/L (100,000 cells/μL) (without transfusion within 2 weeks prior to Cycle 1, Day 1).

– Hemoglobin ≥ 90 g/L (9.0 g/dL).

  Patients may be transfused or receive erythropoietic treatment to meet this criterion. Following transfusion, a 2-week washout period is required before Cycle 1, Day 1.

– Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $\leq 2.5 \times$ the upper limit of normal (ULN), with the following exceptions:

  Patients with documented liver metastases: AST and ALT $\leq 5 \times$ULN

  Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN

– Serum bilirubin $\leq 1.5 \times$ ULN

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 × ULN
    - This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
- Calculated creatinine clearance (CrCl) ≥ 30 mL/min.
- Negative hepatitis B surface antigen (HBsAg) test at screening.
- Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:
- Negative total hepatitis B core antibody (HBcAb) test at screening, or
- Positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) deoxyribonucleic acid (DNA) test at screening.
- The HBV DNA test must be performed for patients who have a negative HBsAg test, a negative HBsAb test, and a positive HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV ribonucleic acid (RNA) test at screening.
- The HCV RNA test must be performed for patients who have a positive HCV antibody test.
- Patients with treated asymptomatic CNS metastases are eligible, provided that all of the following criteria are met:
- The metastases are limited to the supratentorial region or cerebellum (i.e., no metastases to midbrain, pons, medulla, or spinal cord are allowed)
- No ongoing requirement for corticosteroids as therapy for CNS disease
- No stereotactic radiation within 7 days or whole-brain radiation or neurosurgical resection within 14 days before the start of study treatment
- No evidence of interim progression between the completion of CNS directed therapy and the screening radiographic study

    Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Patients with a history of autoimmune disease (Appendix 3) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:
- Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks;
- Patients with a history of serious or life threatening immune-mediated events;

- Patients with more than one concomitant autoimmune disease at the time of study entry, unless one of them is:

    Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone;

    Controlled Type I diabetes mellitus on a stable dose of insulin regimen;

- A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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).

  The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year, during the treatment period and for at least 5 months after the final dose of atezolizumab or 6 months after the final dose of nab-paclitaxel, whichever is later. In addition, women must refrain from donating eggs during the same time period.

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

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, copper intrauterine devices (IUDs), and the combination of condom and spermicide. Hormonal contraceptives that inhibit ovulation, and hormone-releasing IUDs may be used in women with HR-negative tumors only.

  Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the final dose of any component of the study treatment. Men must refrain from donating sperm during this same period.

  Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

4.1.2 Exclusion Criteria

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

Cancer-Specific Exclusion Criteria:

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to the first dose of study treatment (Cycle 1, Day 1).
- Leptomeningeal carcinomatosis or any symptomatic CNS metastases
- Uncontrolled symptomatic pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients requiring narcotic 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 the first dose of study treatment (Cycle 1, Day 1). Patients should be recovered from the effects of radiation. There is no minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the first dose of study treatment (Cycle 1, Day 1).
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal event and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than breast cancer within 5 years prior to the first dose of study treatment (Cycle 1, Day 1), with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer).

General Medical Exclusion Criteria:

- Pregnancy or lactation
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver

disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome).

- Significant cardiovascular disease such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to the first dose of study treatment (Cycle 1, Day 1), unstable arrhythmias, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) <40% will be excluded.

  Patients with known coronary heart disease, congestive heart failure not meeting the above criteria, or LVEF between 40% and <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Severe infection within 4 weeks prior to the first dose of study treatment (Cycle 1, Day 1), including, but not limited to, hospitalization for complications of infection, bacteraemia, severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety.
- Treatment with oral or IV antibiotics within 2 weeks prior to initiation of study treatment (Cycle 1, Day 1).

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation, urinary tract infection or for dental extraction) are eligible.
- Major surgical procedure within 28 days prior to the first dose of study treatment (Cycle 1, Day 1), or anticipation of the need for a major surgical procedure during the course of the study (other than diagnostic procedures).

  Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Treatment with investigational therapy within 4 weeks prior to Cycle 1, Day 1.
- Known hypersensitivity to nab-paclitaxel or any of the excipients.
- Positive human immunodeficiency virus (HIV) test at screening, unless the patient meets all of the following conditions:
  - Stable on anti-retroviral therapy
  - CD4 count ≥200/mL
  - Undetectable viral load.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.

Exclusion Criteria Related to Atezolizumab:

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.
- Prior allogenic stem cell or solid organ transplantation.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan.

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Current treatment with anti-viral therapy for HBV.
- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to the first dose of study treatment (Cycle 1, Day 1), or anticipation that such a live, attenuated vaccine will be required during atezolizumab treatment or within 5 months following the final dose of atezolizumab

  Patients must agree not to receive live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to the first dose of study treatment (Cycle 1, Day 1), during treatment, or within 5 months following the last dose of atezolizumab.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies (including anti–CTLA-4 antibodies), except for anti–PD-1 or anti–PD-L1 antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to the first dose of study treatment (Cycle 1, Day 1).
- Only in patients without autoimmune disease: Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to the first dose of study treatment (Cycle 1, Day 1), or anticipated requirement for systemic immunosuppressive medications during the study

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study.

  Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI.

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label (non-blinded), single arm safety study in which all patients will receive atezolizumab in combination with nab-paclitaxel.

Consecutive consenting patients will be enrolled upon confirmation of eligibility and registration completed in the interactive voice/web response system (IxRS).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

Atezolizumab and nab-paclitaxel are considered investigational medicinal product (IMPs) in this study. All IMPs will be provided by the study sponsor until criteria for study drug or study treatment discontinuation are met (e.g., disease progression, intolerance, etc.).

Non-investigational medicinal products (NIMPs) used in the study include premedication (see Section 4.4.1.1), medications that may be administered to manage adverse events (see Section 4.4.1.2), and other permitted concomitant medications (see Section 4.4.1.3).

The term "study drug" is used throughout this protocol to refer to atezolizumab. The term "study treatment" refers to all protocol-mandated treatment (atezolizumab plus nab-paclitaxel).

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, 14-mL glass vial. The vial contains 14 mL (840 mg) of atezolizumab solution.

Atezolizumab vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Vials should not be used beyond the expiration date provided by the manufacturer. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. Any unused portion of drug left in a vial should be discarded. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Further details on the storage and preparation of atezolizumab are provided in the Atezolizumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.2 Nab-Paclitaxel

Nab-paclitaxel monotherapy is approved for the treatment of mBC in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. However, the nab-paclitaxel dosing regimen used in this study (100 mg/m^2 via IV infusion on Days 1, 8, and 15 of every

28-day cycle) is not approved in patients with TNBC. Therefore, nab-paclitaxel will be considered an IMP in this study and provided by the Sponsor.

Refer to the local prescribing information for nab-paclitaxel for information on the formulation, storage, and handling.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Enrolled patients will receive treatment according to the following regimen:

Atezolizumab 840 mg administered via IV infusion on Days 1 and 15 of every 28-day cycle (see Section 4.3.2.1) in combination with nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle (see Section 4.3.2.2).

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

In the absence of PD or unacceptable toxicity, study treatment will continue until the EOS.

Patients must discontinue all study treatment upon determination of PD per RECIST v1.1. Consistent with RECIST v1.1, in case of equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; 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.

Atezolizumab and nab-paclitaxel may be discontinued for toxicity and re-started independently of each other in the absence of PD.

Details on treatment administration, including any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose or medication error, with or without any associated adverse events, should be reported as described in Section 5.3.5.11.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator. The first dose (Cycle 1, Day 1) will be administered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Day 15: Atezolizumab may be administered on Days 15–18 of each cycle. Nab-paclitaxel administration must occur on the same day with the atezolizumab infusion (see Section 4.3.2.2 and Appendix 1).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to

manage potentially serious reactions. For anaphylaxis precautions, see Appendix 4. Atezolizumab infusions will be administered per the instructions outlined in Table 2. For the first infusion of atezolizumab, no premedication will be administered. However, should the patient experience infusion-related reaction(s) during any infusion, premedication with antihistamines will be administered for subsequent infusions at the discretion of the treating physician.

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 the infusion. • Atezolizumab 840 mg (14 mL in 250 mL NaCl) 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, antipyretic medications, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

Dose reduction of atezolizumab is not permitted. Guidelines for atezolizumab dosing interruption or discontinuation are included in Appendix 8.

Guidelines for management of specific adverse events, including infusion-related reactions (IRRs) are also provided in the Appendix 8.

4.3.2.2 Nab-Paclitaxel

Nab-paclitaxel will be administered at the 100 mg/m^2 dose via 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle (3-weeks-on, 1-week-off schedule). On days of scheduled infusions of atezolizumab and nab-paclitaxel (i.e., Day 1 and Day 15 of every cycle), nab-paclitaxel is to be administered after the atezolizumab infusion. Day 8: Nab-paclitaxel may be administered on Days 8–11 of each cycle. Day 15: Nab-paclitaxel may be administered on Days 15–18 of each cycle, on the same day with the atezolizumab infusion (see Section 4.3.2.1 and Appendix 1). Doses of nab-paclitaxel should not be administered more frequently than every 7 days.

Sites should follow their institutional standard of care for determining the nab-paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Corticosteroid or antihistamine premedication is not required with the use of nab-paclitaxel, and should not be used.

Guidelines on nab-paclitaxel dose modifications, interruptions, and discontinuations due to toxicity are provided in Appendix 7.

Any overdose or incorrect administration of paclitaxel should be noted on the Nab paclitaxel Administration eCRF and on the Adverse Event eCRF as described in Section 5.3.5.11.

4.3.3 Additional Medication

Other non-investigational medicinal products (NIMPs) used in the study include premedication, medications that may be administered to manage adverse events, and other permitted concomitant medications.

All concomitant medications will be recorded on the eCRF.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (atezolizumab and nab-paclitaxel) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Unused IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or 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.

Refer to the pharmacy manual for further information on IMP handling, storage, and accountability.

4.3.5 Continued Access to Atezolizumab

The Sponsor will offer continued access atezolizumab 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 after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued atezolizumab 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 after completing the study if any of the following conditions are met:

- Atezolizumab 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 wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of atezolizumab or data suggest that atezolizumab is not effective for mTNBC
- The Sponsor has reasonable safety concerns regarding atezolizumab as treatment for mTNBC
- Provision of atezolizumab 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.

Between the treatment discontinuation and the last follow-up visit, only new anti-cancer treatment and medications to treat AEs will be recorded.

4.4.1 Permitted Therapy

4.4.1.1 Premedication

For the first infusion of atezolizumab, no premedication will be administered. However, should the patient experience an IRR during any infusion, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for subsequent infusions at the discretion of the treating physician.

Corticosteroid or antihistamine premedication is not required with the use of nab-paclitaxel, and should not be used.

4.4.1.2 Treatment of Infusional Adverse Events

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine (or equivalent substitutes, per local practice), and/or famotidine or another H_2 receptor antagonist, per standard practice. Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

4.4.1.3 Other 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)
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Bisphosphonates or denosumab for the prevention of skeletal events
- Inactivated influenza vaccinations
- COVID-19 vaccines
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma

- Low-dose corticosteroids (≤10 mg prednisone equivalent per day) administered for orthostatic hypotension or adrenocortical insufficiency
- Anticonvulsants at a stable dose, e.g., for patients with CNS metastases
- Narcotic pain medication is permitted as long as the patient is on a stable regimen at study entry
- Radiotherapy (e.g., treatment of known bone metastases), as outlined below:
    - Candidate lesions for radiotherapy must be decided prior to study entry.
    - It is not required to hold atezolizumab during palliative radiotherapy; nab-paclitaxel should be interrupted per institutional standard of care.
    - Patients who receive radiotherapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.
- Local therapy (e.g., surgery, stereotactic radiosurgery, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary and prohibited therapies related to atezolizumab or additional restrictions related to nab-paclitaxel (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice.

Patients who use contraceptives should continue their use during the treatment period and for at least 5 months after the final dose of atezolizumab or 6 months after the final dose of nab-paclitaxel; refer to Section 4.1.1.

4.4.2 Prohibited and Cautionary Therapy

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies have been conducted for atezolizumab, and there are no known PK interactions with other medicinal products.

Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (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.

Additional medications that are prohibited while the patient is receiving study treatment, and their respective washout periods prior to commencement of study treatment are listed in Table 3.

Systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF 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 AEs when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are described in Appendix 8.

Table 3 Anti-Cancer Treatment-Free Intervals and Prohibited Medications and Treatments

Prior Anti-Cancer Therapy	Minimum Treatment-Free Interval Period prior to Cycle 1, Day 1
Prior taxane-based chemotherapy (neo/adjuvant)	12 months
Prior PD-1/PD-L1–based regimen (neo/adjuvant)	12 months
Capecitabine, non-taxane chemotherapy (neo/adjuvant)	6 months
Adjuvant hormonal therapy	2 weeks
Abatacept or belatacept treatment	>8 weeks
Other therapy intended for the treatment of cancer (including, but not limited to, radiotherapy, and herbal therapy)	4 weeks or five drug-elimination half-lives of the drug (whichever is longer)
Prohibited Medication/Class	**Minimum Washout Period prior to Cycle 1, Day 1**
Any investigational therapy	4 weeks
Prior treatment with oral or IV antibiotics	2 weeks
Immunomodulatory agents (e.g., interferons or IL 2) [a]	4 weeks or five drug-elimination half-lives of the drug (whichever is longer)
Any live, attenuated vaccine (e.g., FluMist®) [b]	4 weeks
Stereotactic radiation for CNS metastases Whole-brain radiation or neurosurgical resection for CNS metastases	1 week 2 weeks

[a] These agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.

[b] Any live, attenuated vaccine is prohibited within 28 days prior to Cycle 1 Day 1, during treatment, and within 5 months following the last dose of atezolizumab.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with the study treatment. The Medical Monitor is available to advise if questions arise regarding medications not listed above.

The concomitant use of herbal therapies is generally not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, their use during the study is allowed at the discretion of the investigator.

4.4.3 Additional Restrictions Related to Nab-Paclitaxel

The metabolism of paclitaxel is catalysed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. The pharmacokinetics of paclitaxel were shown to be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. Therefore, caution should be exercised when nab-paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., grapefruit juice, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4. In addition, caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Granulocyte-colony stimulating factor (G-CSF) as haematopoietic support is permitted for patients receiving paclitaxel and nab-paclitaxel. The primary prophylaxis should be administered per the ASCO, European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors, such as age ≥65 years, previous chemotherapy or radiation therapy, preexisting neutropenia or bone marrow involvement, infection, comorbidities, etc. (Aapro et al. 2011; Crawford et al. 2010; Smith et al. 2015).

Consistent with the latest ASCO recommendations (Smith et al. 2015), and results of meta-analyses of primary G-CSFs in adults undergoing chemotherapy for a solid tumor or lymphoma (Pinto et al, 2007; Cooper et al, 2011; Renner et al, 2012; Mitchell et al. 2016), both conventional (e.g., filgrastim) and long-acting, or pegylated (e.g., pegfilgrastim) G-CSFs may be used for the prevention of treatment-related febrile neutropoenia. The choice of agent will be at the discretion of the investigator, depending on the clinical situation and institutional standard of care practice.

Anti-emetics, anti-allergic measures, and other treatments for concomitant paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the local prescribing information for paclitaxel.

Refer to the local prescribing information (label) for nab-paclitaxel for all boxed warnings and contraindications.

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.

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 or evaluations. Informed Consent Forms for enrolled patients and for patients who are screening failures will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrolment. 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 stage, date of diagnosis, prior cancer therapies and procedures), reproductive status, smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to screening to the treatment discontinuation visit will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

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

Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion (see Table 2). In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1). After discontinuation of nab-paclitaxel, vital signs no longer need to be measured on Day 8 of subsequent treatment cycles.

Vital signs abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

Tumor assessments will be performed [redacted] thereafter, until PD per RECIST v1.1, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening/baseline and during the study in accordance with RECIST v1.1. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.5.1 Screening/Baseline Tumor Assessments

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

Radiologic imaging performed during the screening period should consist of the following:

- Initial screening assessments must include CT scans (with oral/IV contrast unless contraindicated) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. A non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If a CT scan for tumor assessment is performed using a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.
- Bone scan or PET scan should be performed to evaluate for bone metastases;
- A CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. If CNS metastases are detected by CT scan, an MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis. Patients with active or untreated CNS metastasis are not eligible for this study (see Section 4.1.2 for CNS-related exclusion criteria);
- CT scans of the neck should also be performed if clinically indicated during the screening period;
- At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

4.5.5.2 On-treatment Tumor and Response Evaluations

All measurable and evaluable lesions identified at screening/baseline (as listed in Section 4.5.5.1) 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), and the results must be reviewed by the investigator before dosing at the next cycle.

Tumor assessments will be performed according to the specified schedule regardless of treatment delays. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. If the initial screening bone scan or PET scan does not show evidence of bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion.

Evaluation of tumor response will be completed by the investigator based on physical examinations, CT scans, and other modalities, per RECIST v1.1 (see Appendix 2). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

If treatment is discontinued prior to disease progression per RECIST v1.1 (e.g., due to study treatment–related toxicity), tumor response assessment should continue to be performed per the schedule specified in Appendix 1. During the post-treatment follow-up period, only patients with no PD will undergo tumor assessments.

4.5.6 Safety Laboratory Samples

An overview of the standard safety laboratory and other sampling requirements is provided below.

All samples for laboratory tests will be sent to the study site's local laboratory for analysis:

- Haematology: red blood cell (RBC) count, haemoglobin, haematocrit, platelet count, white blood cell (WBC) count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- Chemistry panel (serum or plasma): blood urea nitrogen (BUN) or urea, creatinine, bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, calcium, glucose, total bilirubin, ALT, AST, ALP, total protein, albumin, and lactate dehydrogenase (LDH); in addition, magnesium and phosphorus should be tested at screening, and thereafter only as clinically indicated.

  The Cockcroft-Gault formula (see Appendix 6) will be used to calculate CrCl. Patients must have a CrCl ≥ 30 mL/min to be eligible for enrolment.
- Coagulation: INR, and aPTT
- Thyroid-function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4).
- Pregnancy test

  A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1. On-study pregnancy tests performed before each treatment cycle and at treatment discontinuation can be conducted with serum or urine. 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

In addition, all patients will be tested for HIV antibody, HBsAg, HBsAb, total hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) locally during screening. In patients with a negative HBsAg and positive HBcAb serology, HBV deoxyribonucleic acid (DNA) must also be collected prior to enrolment to determine if the patient has an active HBV infection. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.

4.5.7 Tumor Tissue Samples

Tumor tissue samples, collected prior to enrolment will be evaluated locally for PD-L1, ER/PgR, and HER2 status, to confirm eligibility. The FFPE tumor specimens will be preferably obtained from metastatic or locally advanced tumor or, if clinically not feasible, archival samples from the primary tumor or the most recent FFPE tumor biopsy sample will also be allowed for screening. Given the slightly lower expression of PD-L1 in metastatic tissue (Rugo et al. 2019), if the metastatic specimen is negative for PD-L1 expression, consider retesting using archival tissue from primary tumor.

A FFPE tissue block, or alternatively 6 freshly cut, unstained tissue sections of the screening tissue sample on which PD-L1 positivity has been determined locally, needs to be submitted for central re-testing of PD-L1 tumor status by VENTANA SP142 IHC assay. Tissue samples must be fixed with 10% buffered formalin for at least 6 hours and up to a maximum of 72 hours.

Acceptable tumor sample collection methods include core needle biopsies from deep tumor tissue (3 cores embedded into one block if clinically feasible), or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. FFPE tumor specimens in paraffin blocks are preferred. Fine needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable. The FFPE tumor tissue should be of good quality based on total and viable tumor content.

PD-L1–positive status (PD-L1 expression ≥1% on tumor-infiltrating ICs as percentage per tumor area, assessed by IHC) will be determined as follows:

- Locally using the VENTANA PD-L1 SP142 IHC assay, to determine eligibility. If multiple tumor specimens are available, patients may be eligible if at least one specimen is evaluable for PD-L1 testing and shows PD-L1 expression on ≥1% ICs; the highest score measured will be used as the PD-L1 score for patient selection;
- Centrally, using the VENTANA PD-L1 SP142 IHC assay, to confirm PD-L1-positive tumor status, and to evaluate the concordance between local and central laboratory testing.

Negative ER/PgR status (defined as <1% of tumor cells expressing ER and PgR hormonal receptors by IHC) must be confirmed in at least one tumor sample (primary and/or metastatic) using a validated test as per the current ASCO-CAP guideline (Hammond et al. 2010; Allison et al. 2020). HER2 negativity (defined as IHC 0, IHC 1+ or IHC2+/ISH–), will be confirmed using a validated test as per the current ASCO-CAP guideline (Wolff et al. 2018).

If the patient provides optional consent for storing samples in the Research Biosample Repository (RBR) for future, non–protocol-defined exploratory research (see Section 4.5.9), the samples will be stored until no longer needed or used up.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analysed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples.

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

4.5.8 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) is required at screening and thereafter when clinically indicated; see Appendix 1. ECGs should be performed prior to other procedures scheduled at that same time (e.g., blood draws). ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised 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 specimens will be analysed to achieve the following objectives:

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

4.5.9.2 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 Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 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 and locally advanced or metastatic TNBC: leftover FFPE tissue.

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (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).

4.5.9.4 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.

4.5.9.5 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 Sample Informed Consent/Withdrawal eCRF.

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

4.5.9.6 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. 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 Sample Informed Consent/Withdrawal 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.

4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorised use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and/or nab-paclitaxel) 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 study treatment is continued
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease 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 via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent, or the Sponsor terminates the study).

4.6.2 Patient Withdrawal from the Study

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

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

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, 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 enrolment 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 given in combination with nab-paclitaxel in completed and ongoing studies. The anticipated important safety risks are outlined below; see Section 5.1.1 (atezolizumab), Section 5.1.2 (nab-paclitaxel), and Section 5.1.3 (atezolizumab in combination with nab-paclitaxel).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and nab-paclitaxel will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 7 and Appendix 8. Refer to Sections 5.2, 5.3, 5.4, 5.5, and 5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Safety assessments will include regular evaluation of AEs and conduct of physical examinations, vital signs, and clinical laboratory tests (haematology, blood chemistry, thyroid hormones). Adverse events will be graded according to the NCI CTCAE v5.0.

After initiation of study treatment, all adverse events (regardless of relationship to study drug) 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. Serious adverse events and AESI 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 the end of the reporting period for SAEs and AESI (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. Follow-up for new anti-cancer therapy and survival will continue for up to [redacted] after the last patient is enrolled in the study.

An IMC will be established for the study to review all AEs, SAEs, and AESI and cumulative safety data throughout the study. Details of the composition of the IMC, the safety review plan and procedures for data review will be provided in the IMC Charter.

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., ASCO or European Society for Medical Oncology).

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab (TECENTRIQ™) is currently approved in several countries around the world (including the USA and the EU) for the treatment of locally advanced or metastatic urothelial carcinoma, NSCLC, extensive-stage SCLC (in combination with carboplatin and etoposide), PD-L1–positive unresectable locally advanced or metastatic TNBC (in combination with nab-paclitaxel), unresectable or metastatic hepatocellular carcinoma (in combination with bevacizumab), BRAF V600 mutation–positive unresectable or metastatic melanoma (in combination with cobimetinib and vemurafenib), *and unresectable or metastatic alveolar soft part sarcoma*.

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. The risks associated with atezolizumab include IRRs and the following immune-mediated events: 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 (SCARs). In addition, immune-mediated reactions may involve any organ system and lead to HLH. Refer to Appendix 8 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 Nab-Paclitaxel

In clinical studies involving patients with breast cancer, the most common adverse reactions, occurring in ≥10% of patients receiving nab-paclitaxel included alopecia [>80%], bone marrow suppression (most commonly neutropenia [79%], leukopenia [71%], anemia [46%], lymphopenia [45%]), peripheral neuropathy [68%], fatigue/asthenia [40%], arthralgia [32%], nausea [29%], diarrhea [25%], myalgia [24%]. Other very common adverse reactions included: thrombocytopenia, rash, anorexia, pyrexia, neuropathy, hypoaesthesia, paraesthesia, vomiting, constipation, stomatitis.

Warnings related to nab-paclitaxel use include rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, bone marrow suppression (primarily neutropenia, which is dose dependent and dose limiting), sensory neuropathy, sepsis, febrile neutropenia, pneumonitis, hepatic

impairment, cardiotoxicity (rare cases of congestive heart failure and left ventricular dysfunction) and eye disorders (cystoid macular edema). Patients should not be retreated with subsequent cycles of nab-paclitaxel until neutrophils recover to >1500 cells/mm^3 and platelets recover to >100,000 cells/mm^3. Nab-paclitaxel should not be administered to patients with total bilirubin >5 × ULN or AST >10 × ULN. All patients should be closely monitored for signs and symptoms of pneumonitis, cardiac events and impaired vision; a confirmed diagnosis of pneumonitis or cystoid macular edema require permanent discontinuation of nab-paclitaxel, and prompt initiation of appropriate treatment and supportive measures.

Uncommon cases (<1 in 100 exposed patients) of haemolytic uraemic syndrome, and very rare cases (<1 in 10,000 exposed patients) of severe inflammation/eruption of the skin and mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have also been reported.

In addition, in the postmarketing setting, there have been reports of cranial nerve palsies, vocal cord paresis, cystoid macular oedema, tumor lysis syndrome, and scleroderma during treatment with nab-paclitaxel, as well as reports of palmar-plantar erythrodysaesthesiae in some patients previously exposed to capecitabine.

Guidelines for nab-paclitaxel dosing modifications, interruptions, and discontinuations are provided in Appendix 7. Other nab-paclitaxel–specific restrictions are detailed in Section 4.4.3.

For further details regarding the safety profile of nab-paclitaxel, including management of toxicities, refer to the local prescribing information.

Patients will be monitored for nab-paclitaxel-related adverse events throughout the study.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Nab-Paclitaxel

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and nab-paclitaxel: rash, pulmonary events, and liver enzyme elevations. In the IMpassion130 study, the following AESI (all grades) occurred at a higher frequency in the atezolizumab plus nab-paclitaxel vs placebo plus nab-paclitaxel groups: immune-mediated rash (36% vs. 26%, respectively), immune-mediated hypothyroidism (18% vs. 4%, respectively), immune-mediated hyperthyroidism (5% vs 1%, respectively), and immune-mediated pneumonitis (4% vs. <1%, respectively) (WO29522 Update Clinical Study Report WO29522, Report Number 1100481; Roche data on file).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavourable 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 5.3.5.8 and 5.3.5.9 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 SAE 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 5.3.5.10)
- 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.

SAEs 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)

AESI 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). AESI 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 5.3.5.5.1)
- 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, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune haemolytic anaemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Myositis
- Myopathies, including rhabdomyolysis

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, 5.5, and 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 (regardless of relationship to study drug) 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. Serious adverse events and AESI 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 (defined as 90 days after the final dose of study treatment) 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 AE severity grading scale for the NCI CTCAE v5.0 will be used for assessing AE severity. Table 4 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 4 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

Causality will be assessed individually for each protocol-mandated therapy.

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 5):

- 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 5 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 fulfils the criteria specified below. Evidence exists that the adverse event has an aetiology 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).

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 AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

AEs that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome"). Ambiguous terms such as "systemic reaction" should be avoided. Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experienced both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 8.

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal haemorrhage 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 AEs 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 AE 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 SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE 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 AE. A laboratory test result must be reported as an AE 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 hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

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 AEs).

5.3.5.5.1 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST >3×baseline value in combination with total bilirubin >2×ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST >3×baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a SAE or an AESI (see Section 5.4.2).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE 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 AE.

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 AEs).

5.3.5.7 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 unresectable locally advanced or mTNBC 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). An IMC will monitor the safety data (including 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 on the Long-Term Survival Follow-Up eCRF, as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of TNBC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. 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.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE 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 AE or a SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)
- 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 AE
- 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 SAE, but should be reported as an AE instead:

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

5.3.5.11 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria or qualifies as an AESI, 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, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

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

5.4 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:

- SAEs (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- AESI (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 SAEs and AESI, 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 SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will also 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 the 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 SAEs 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, SAEs and AESI will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy,

whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial 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 SAEs that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within **5 months** after the final dose of atezolizumab or within **6 months** after the final dose of nab-paclitaxel, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within **5 months** after the final dose of atezolizumab or within **6 months** after the final dose of nab-paclitaxel, whichever is longer. 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. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted

by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a SAE, 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 AE.

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 SAE, 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 AE 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 AEs (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, by following the reporting instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For SAEs, AESI, 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 SAEs and AESI (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 SAE 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 SAEs and AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

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

- Atezolizumab Investigator's Brochure
- EU Summary of Product Characteristics (SmPC) for nab-paclitaxel

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document. Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

MO39874 is a global, open-label, Phase IIIb, single arm study to evaluate the safety of atezolizumab when given in combination with nab-paclitaxel in patients with previously untreated, unresectable locally advanced or metastatic PD-L1–positive TNBC.

All analyses will be completed on the safety population, defined as all enrolled patients who have received at least one dose of study treatment.

A per-protocol population will not be defined for this study. However, all major deviations (at study entry and on study) will be summarised and reported.

The primary analysis and reporting of the study will occur after LPLV, approximately [redacted] after the last patient was enrolled.

Full details of the planned study analyses will be presented in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

This is a single-arm safety study. There are no formal statistical hypotheses and all analyses will be descriptive. The results for the primary safety variables will be presented using percentages and corresponding 95% Clopper-Pearson CIs.

A sample size of approximately 180 PD-L1–positive TNBC patients is planned for the study. For the purpose of the estimation of sample size, the incidence of treatment-emergent Grade ≥3 AEs, and the incidence of treatment-emergent Grade ≥2 immune-mediated AEs (imAEs) were chosen as an endpoints of primary interest. [redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, study drug administration, reasons for study drug discontinuation and discontinuation from the study will be summarized overall, for all enrolled patients. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race/ethnicity, stratification variables and other relevant baseline characteristics will be summarised using means, standard deviations (SDs), medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

The baseline value of any non-efficacy variable will be defined as the last available value recorded on or prior to the first administration of any study treatment. The baseline value of any efficacy variable will be defined as the last available value recorded prior to

enrolment. Enrolment is defined as the date and time when the patient's eligibility for the study is confirmed and registration is completed in the IxRS.

6.4 SAFETY ANALYSES

Safety will be summarized by descriptive statistics.

6.4.1 Primary Analysis of Safety

The primary endpoint of the study is the incidence of treatment-emergent Grade ≥3 AEs, and the incidence of treatment-emergent Grade ≥2 imAEs. Verbatim descriptions of AEs will be mapped to MedDRA terms, and graded according to the NCI CTCAE v5.0. For each patient, multiple occurrences of the same event will be counted once at the maximum severity.

The results for the primary safety variables will be presented by descriptive statistics in frequency tables and the corresponding 95% Clopper-Pearson CIs will be provided, as applicable.

6.4.2 Secondary Analyses of Safety

Secondary safety endpoints include the incidence of all treatment-emergent AEs and SAEs.

Other safety variables studied will include the following:

- Drug exposure (treatment duration, number of doses, dose intensity and dose modifications/discontinuations)
- AESI
- AEs leading to study drug discontinuation or interruption
- Changes from baseline in vital signs measurements
- Changes from baseline in select laboratory parameters
- Deaths and cause of death

Treatment exposure, discontinuation rate, and cause of death will be described in frequency tables. When appropriate, median time on treatment and 95% CI will be estimated by the Kaplan-Meier approach or using descriptive statistics, presenting mean, median, quartiles, minimum, maximum and standard deviation.

The incidence of AEs will be summarized by frequency tables, with corresponding 95% Clopper-Pearson CIs, as applicable.

Changes in vital signs from baseline will be tabulated and presented graphically when applicable.

Relevant laboratory values will be summarised by worst shift, with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate. Worst grades for laboratory parameters and newly occurring Grade 3 and 4 laboratory values during treatment will be summarized by frequency tables.

Concomitant medications recorded during the study will be summarized by frequency tables.

Further details will be provided in the SAP.

6.5 EFFICACY ANALYSES

6.5.1 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- OS
- PFS

Both endpoints (OS and PFS) will be analyzed in the ITT population and in the subset of patients with centrally confirmed PD-L1–positive tumor status.

OS is defined as the time from initiation of study treatment to death from any cause. Patients who are still alive at the time of analysis (clinical cutoff) and patients who are lost to follow-up will be censored at their last clinical assessment date or, if this is not available, at the date of enrolment + 1 day.

PFS is defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be assessed by the investigator according to RECIST v1.1. Patients without a PFS event will be censored at the date of their last evaluable tumor assessment or, if this is not available, at the date of enrolment + 1 day.

OS and PFS will be presented graphically using the Kaplan-Meier method. The median and the corresponding 95% CI will be reported. Kaplan-Meier methodology will be used to estimate the 12-, 24-, and [redacted] OS rates, and to estimate the 6-, 9- and 12-month PFS rates.

6.5.2 Exploratory Efficacy Endpoints

Exploratory analyses of the following endpoints will be completed:

- ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved a CR or a PR as determined by the investigator using RECIST v1.1

  Patients without a post-baseline tumor assessment will be considered non responders. The number and proportion of responders and non-responders will be presented with the corresponding Clopper-Pearson 95% CIs.

- DCR, defined as the sum of the CR, PR and SD rates, will be presented along with the 95% Clopper-Pearson CIs
- DoR, defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first

  Estimates for DoR will be obtained using the Kaplan-Meier approach.
- [redacted]

6.6 SUBGROUP ANALYSES (EXPLORATORY)

As part of the exploratory analyses, select safety and efficacy endpoints may be described within particular subgroups, provided that sample sizes are sufficient [redacted] within each subgroup category. Subgroups of interest include the following:

- Presence of CNS metastases (yes vs. no)
- ECOG Performance Status (0 or 1 vs. 2)
- Prior anti-cancer treatment (yes vs. no)
- Prior anti-cancer treatment with PD-1/PD-L1 inhibitor (yes vs. no)
- Prior use of taxane or non-taxane therapy in (neo)adjuvant settings.

Additional details will be provided in the SAP.

[redacted]

6.8 BIOMARKER ANALYSES

6.8.1 Exploratory Biomarker Analysis

Exploratory biomarker analyses (on tumor tissue) will be performed to evaluate the inter-observer concordance between PD-L1 status determined by local vs central laboratory testing, using the VENTANA PD-L1 SP142 Assay.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Central laboratory data will be sent to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location. Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms (or to a significant new information/findings 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.

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 9.4)

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. 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. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann La Roche Ltd.

A total of approximately 180 patients will be enrolled at approximately 90 sites in approximately 15 countries from Europe, Asia, Africa, as well as Central and South America over approximately 19 months. Screening and enrollment will occur through an IxRS.

Project Management, data management, day-to-day clinical monitoring, and statistical programming responsibilities will be outsourced.

All laboratory testing will be completed locally. Accredited local laboratories will be used for routine safety monitoring; local laboratory ranges will be collected.

Clinical data will be captured using standard eCRFs, the design of which will be consistent with the eCRFs of other atezolizumab clinical trials.

Responsibilities of the study SC and the IMC will be provided in the respective committee charters.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Assessment Day (Window)	Screening	All Cycles			Treatment Discontinuation Visit	Follow-Up Every 3 months (±21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a]	Day 15 [a]	≤30 Days after Last Dose	
Written informed consent [b]	x					
Review of eligibility criteria	x					
Demographics [c]	x					
Medical history [c]	x					
Head CT or MRI	x					
HIV, HBV, and HCV serology [d]	x					
Complete physical examination [e]	x					
Limited physical examination [f]		x			x	
ECOG performance status [f]	x	x			x	
Vital signs [g]	x	x	x [g]	x	x	
Weight	x	x			x	
Height	x					
12-lead electrocardiogram [h]	x	As clinically indicated				
Tumor assessments [i]	[redacted]					until PD
Haematology and serum chemistry [j, f]	x	x	x	x	x	
Coagulation panel (aPTT, INR)	x	As clinically indicated			x	
Urinalysis [k]	x	As clinically indicated				

Appendix 1: Schedule of Activities

Assessment Day (Window)	Screening	All Cycles			Treatment Discontinuation Visit	Follow-Up Every 3 months (±21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a]	Day 15 [a]	≤30 Days after Last Dose	
Pregnancy test [l] women of child-bearing potential only	x	x			x	
TSH, free T3, free T4	x	Cycle 1 Day 1 and every other cycle thereafter			x	
Concomitant medications [m]	x	x	x	x	x	
Adverse events [n]		x	x	x	x	
Atezolizumab infusion [o]		x		x		
Nab-paclitaxel administration [p]		x	x	x		
Local confirmation of PD-L1, ER/PgR, and HER2 status [q]	x					
Mandatory tumor tissue sample for central confirmation of PD-L1 status [r]	x					
Survival and anti-cancer therapy follow-up [s]						x

aPTT: activated partial thromboplastin time; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; 5 Dimension; ER/PgR: oestrogen/progesterone receptors; FFPE: fixed formalin paraffin embedded; HBcAb= antibody to hepatitis B core antigen; HBsAg=hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: Human Immunodeficiency Virus; INR: international normalized ratio; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; PD-L1: programmed death ligand 1; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone

a. Day 1: Assessments scheduled on the first day of study treatment administration of each cycle should be performed prior to study treatment infusion unless otherwise noted. Assessments may be performed on Day 1 ± 3 days of each treatment cycle after cycle 1. Days 8 and 15: Assessments may be completed within ± 3 days of the visit, apart from local safety laboratory tests (to be completed within ≤ 72 hours prior to the respective visits; see footnote f). However, nab-paclitaxel should not be administered more frequently than every 7 days.

b. Written informed consent is required before performing any study-specific tests or procedures unless these have already been conducted as standard of care. Signing of the Informed Consent Form can occur outside the 28-day screening period.

c. Demographics include age, gender, self-reported race/ethnicity. Medical history includes reproductive status, smoking history, prior surgeries and cancer history (stage, date of diagnosis, prior anti-cancer treatment).

d. HIV antibody, HBV (HBsAg, HBsAb, HBcAb, HBV DNA test) and HCV (HCVAb) tests will be conducted locally. The HBV DNA test will be performed only for patients who have a positive HBcAb test. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.

e. A complete physical examination must be conducted at screening and the treatment discontinuation visit. Symptom-driven physical examinations may be conducted during treatment and may be done ≤ 96 hours of Day 1 treatment, and as clinically indicated.

f. ECOG performance status, limited physical examination, and local laboratory assessments may be obtained within ≤ 96 hours before Day 1 of each cycle. Local laboratory assessments scheduled for Day 8 and Day 15 of each cycle should be completed within ≤ 72 hours prior to the respective visits.

g. Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. After discontinuation of nab-paclitaxel, vital signs no longer need to be measured on Day 8 of subsequent treatment cycles.

h. Standard 12-lead ECG, taken after resting in a supine position for at least 10 minutes.

i. Tumor assessments will be performed [redacted] until PD, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening/baseline and during the study in accordance with RECIST v1.1. Results must be reviewed by the investigator before dosing at the next cycle.

j. Haematology consists of RBC count, haemoglobin, haematocrit, WBC count with differential, and platelet count. Serum chemistry includes BUN, creatinine, sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered standard of care for the region), calcium, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin; in addition, magnesium and phosphorus should be tested at screening, and thereafter only as clinically indicated. Local laboratory test results must be reviewed prior to each study treatment administration.

k. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

l. A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1. On-study pregnancy tests performed before each treatment cycle and at treatment discontinuation can be conducted with serum or urine. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

m. Includes all prescription or over-the-counter medications taken from 7 days prior to screening to the treatment discontinuation visit.

n. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events (SAEs) caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events (AEs) will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any deaths, SAEs,

AESI, or other AEs of concern that are considered related to prior treatment with the study drug. The investigator should follow each SAE and Grade ≥3 AE until the event has resolved to baseline grade, assessed as stable by the investigator, or until the patient withdraws consent or is lost to follow-up. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

o. The first dose of atezolizumab will be delivered over 60±15 minutes; if well tolerated, all subsequent infusions may be delivered over 30±10 minutes. Day 15: Atezolizumab may be administered on Days 15–18 of each cycle. Nab-paclitaxel administration must occur on the same day with the atezolizumab infusion (see also footnote p).

p. Nab-paclitaxel will be administered at the 100 mg/m^2 dose via 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle (3-weeks-on, 1-week-off schedule). On days of scheduled infusions of atezolizumab and nab-paclitaxel (i.e., Day 1 and Day 15 of every cycle), nab-paclitaxel is to be administered after the atezolizumab infusion. Day 8: Nab-paclitaxel may be administered on Days 8–11 of each cycle. Day 15: Nab-paclitaxel may be administered on Days 15–18 of each cycle, on the same day with the atezolizumab infusion (see footnote o). Doses of nab-paclitaxel should not be administered more frequently than every 7 days.

q. Mandatory tumor tissue biopsy collected prior to study enrolment, for local confirmation of PD-L1-positivity. If HER2-negative, and ER/PgR-negative tumor status is not known, this will need to be confirmed before enrollment. The FFPE tumor specimens will be obtained from relapsed metastatic or locally advanced tumor or, if clinically not feasible, archival samples from the primary tumor or the most recent FFPE tumor biopsy sample will also be allowed. Acceptable tumor sample collection methods include core needle biopsies for deep tumor tissue, or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable.

r. A FFPE tissue block, or alternatively 6 freshly cut, unstained tissue sections of the screening tissue sample on which PD-L1 positivity has been determined locally, needs to be submitted for central re-testing of PD-L1 tumor status by VENTANA SP142 assay. Tissue samples must be fixed with 10% buffered formalin for at least 6 hours and up to a maximum of 72 hours.

s. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information until death, withdrawal of consent, loss to follow-up, or until study termination by the Sponsor for a minimum of [redacted] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits. Public information sources (e.g., county records) may also be used to obtain information about survival status only in case the patient withdraws from the study.

Appendix 2
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").

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

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[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.

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, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item

on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

REFERENCE

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

Appendix 3
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease (see table below). Patients with a history of autoimmune disease are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:

1. Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks;
2. Patients with a history of serious or life-threatening immune-mediated events;
3. Patients with more than one concomitant autoimmune disease at the time of study entry, unless one of them is:

a) Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone;

b) Controlled Type I diabetes mellitus on a stable dose of insulin regimen;

c) A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. 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.

Appendix 3: Preexisting Autoimmune Diseases and Immune Deficiencies

Autoimmune Diseases and Immune Deficiencies		
• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anaemia • Autoimmune haemolytic anaemia • 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 • Granulomatosis with polyangiitis • 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 anaemia • 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

Appendix 4
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 intramuscular (preferred route), subcutaneous, 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, if possible.
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 5
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

Appendix 6
Cockcroft-Gault formula

Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula:

For females:

$CrCl = 0.85 \times ((140 - Age) / (Serum\ Creatinine)) \times (Weight / 72)$

For males:

$CrCl = ((140 - Age) / (Serum\ Creatinine)) \times (Weight / 72)$

Where the units are:

Creatinine clearance: mL/minute

Age: years

Weight: kg

Serum Creatinine: mg/dL

Appendix 7
Nab-Paclitaxel Toxicity Management Guidelines

GENERAL CONSIDERATIONS

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

When several toxicities with different grades of severity occur at the same time, the dose interruptions or modifications should be according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab or nab-paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

When treatment is temporarily interrupted because of toxicity caused by atezolizumab or nab-paclitaxel, the treatment cycles will be restarted such that the atezolizumab and nab-paclitaxel infusions remain synchronised.

If it is anticipated that nab-paclitaxel will be delayed by ≥2 weeks, then atezolizumab should be given without the chemotherapy, as long as there is no contraindication.

In general, the start of a cycle may be delayed to allow recovery from toxicities, but there should be no delays within cycles. Cycle length is fixed at 28 days, and dosing on Days 8 and 15 of a cycle may be skipped but should not be delayed outside of the visits' windows specified in the Schedule of Assessments (Appendix 1).

The treating physician may use discretion in accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient.

DOSE MODIFICATIONS AND INTERRUPTIONS

NAB-PACLITAXEL TOXICITY MANAGEMENT GUIDELINES

Haematologic Toxicities

In general, absolute neutrophil count (ANC) must be ≥1500/μL (≥1500 cells/mm^3) and platelet count must be ≥100,000/μL (≥100,000 cells/mm^3) for the patient to receive nab-paclitaxel on Day 1 of any 28-day cycle.

When nab-paclitaxel is administered on Day 1, it should not be administered on Days 8 or 15 of the cycle unless ANC ≥ 500 cells/μL and platelets ≥ 50,000 cells/μL. If Day 1 of a cycle begins with only atezolizumab but without the administration of nab-paclitaxel due to low platelet or ANC levels, nab-paclitaxel should not be administered subsequently within that cycle until ANC ≥1500/μL and platelet count ≥100,000/μL If

the delay in re-starting nab-paclitaxel is >7 days (i.e., counts do not recover until Day 15) dosing should be resumed with applicable reductions according to the criteria in Table A.

If the start of a cycle is delayed (i.e., both atezolizumab and nab-paclitaxel are held) for low counts, postpone Day 1 and resume dosing when counts recover with applicable reductions according to criteria in Table A.

If nab-paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels with applicable dose reductions according to the criteria in Table A.

If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the nab-paclitaxel doses should be permanently reduced as outlined in Table A.

Table A nab-Paclitaxel Permanent Dose Reductions for Haematologic Toxicity

Haematologic Toxicity	Occurrence	Weekly nab-Paclitaxel Dose
Neutropenic fever (nadir ANC < 500/μL with fever > 38°C) or Delay of first administration of nab-paclitaxel in a cycle by > 7 days for nadir ANC < 1500/μL or Nadir ANC < 500/μL for > 7 days	First	75 mg/m^2
	Second	50 mg/m^2
	Third	Discontinue treatment
Nadir platelet count < 50,000/μL	First	75 mg/m^2
	Second	Discontinue treatment

ANC=absolute neutrophil count

Gastrointestinal Toxicities

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

Table B nab-Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity	Grade	Adjusted nab-Paclitaxel Dose as Percentage of Starting Dose
Diarrhea	Grade 4	Discontinue nab-paclitaxel
Oral mucositis/stomatitis	Grade 4	Discontinue nab-paclitaxel
Oral mucositis/stomatitis	Grade 3	1st occurrence: 75 mg/m^2 2nd occurrence: 50 mg/m^2 3rd occurrence: discontinue nab-paclitaxel
Diarrhea	Grade 3	
Nausea/vomiting	Grade 3 or 4	

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs in spite of anti-emetics, the dose should be reduced by 25 mg/m^2 for the next course.

Also refer to Appendix 8 (including Table 3) for guidance on management of gastrointestinal toxicities associated with atezolizumab.

Neurological Toxicities

Nab-paclitaxel should be withheld for Grade 3–4 peripheral neuropathy and may be resumed at reduced doses (see Table C) when peripheral neuropathy recovers to Grade 1 or completely resolves.

Table C nab-Paclitaxel Permanent Dose Reductions for Neurological Toxicity

Neurological Toxicity	Occurrence	Weekly nab-Paclitaxel Dose Modification
Grade 3 or 4 peripheral neuropathy	First	Withhold treatment until resolves to Grade ≤ 1, then resume treatment at 75 mg/m^2
	Second	Withhold treatment until peripheral neuropathy resolves to Grade ≤ 1, then resume treatment at 50 mg/m^2
	Third	Discontinue treatment

Also refer to Appendix 8 (including Table 10) for guidance on management of immune-mediated neurological toxicities associated with atezolizumab.

Hepatic Toxicity

Nab-paclitaxel should be withheld for Grade 3 or 4 hepatic toxicity as specified in Table D.

Table D nab-Paclitaxel Dose Modification for Hepatic Toxicity

Hepatic Toxicity	Nab-Paclitaxel Dose Modification
SGOT (AST) level < 10 × ULN **and** Bilirubin level > ULN to ≤ 1.5 × ULN	No dose modification; proceed with 100 mg/m^2
SGOT (AST) level < 10 × ULN **and** Bilirubin level > 1.5 to ≤ 5 × ULN	Interrupt treatment until SGOT (AST) level < 10 × ULN **and** bilirubin level ≤ 1.5 × ULN, then reduce to 75 mg/m^2 [a] If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
SGOT (AST) or SGPT (ALT) level > 10 × ULN **or** Bilirubin level > 5 × ULN	Discontinue treatment

ULN= upper limit of normal

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement.

Also refer to Appendix 8 (including Table 2) for guidance on management of immune-mediated hepatic toxicities associated with atezolizumab.

Pulmonary events/Pneumonitis

Interstitial pneumonitis has been observed in <1% of patients with nab-paclitaxel monotherapy and 4% with the use of nab-paclitaxel in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis.

nab-Paclitaxel should be permanently discontinued upon ruling out infectious aetiology and making a diagnosis of pneumonitis. Promptly initiate appropriate treatment and supportive measures. Also refer to Appendix 8 (including Table 1) for guidance on management of immune-mediated pulmonary toxicities/pneumonitis associated with atezolizumab.

Infections should be ruled out with routine microbiological and/or immunologic methods.

After ruling out an infectious aetiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary

pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, nab-paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. Nab-paclitaxel may be resumed at reduced doses (75 mg/m^2 after first occurrence, and 50 mg/m^2 after second occurrence) when toxicity recovers to Grade 1 or completely resolves. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

Refer to the local nab-paclitaxel prescribing information for further details.

PERMANENT TREATMENT DISCONTINUATION

NAB-PACLITAXEL

Nab-paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or generalised urticaria; these events should be treated with aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with nab-paclitaxel.

In addition, nab-paclitaxel should be permanently discontinued upon ruling out infectious aetiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. Consideration may be given to performing pulse oximetry and pulmonary function tests to confirm respiratory and ventilation compromise in patients with suspected pneumonitis. Also refer to Appendix 8 (including Table 1) for guidance on management of immune-mediated pulmonary toxicities/pneumonitis associated with atezolizumab.

Refer to the local nab-paclitaxel/paclitaxel prescribing information for further details.

MANAGEMENT GUIDELINES

Additional guidelines for management of patients who experience specific adverse events associated with atezolizumab are provided in Appendix 8.

Appendix 8
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

ATEZOLIZUMAB DOSE MODIFICATIONS AND INTERRUPTIONS

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

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.

PERMANENT DISCONTINUATION OF ATEZOLIZUMAB

Atezolizumab should be discontinued in case of the following events:

- Recurrent pneumonitis (any grade), Grade 2 pulmonary event that has not resolved to Grade ≤1 within 12 weeks, recurrent Grade 2 pulmonary event, or any Grade 3 or 4 pulmonary event;
- Grade 2 hepatic event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 hepatic event;
- Grade 2 or 3 diarrhea or colitis that has not resolved to Grade ≤1 within 12 weeks, or any Grade 4 diarrhea or colitis;
- Life-threatening immune-mediated hyperthyroidism;
- Grade 2 to 4 symptomatic adrenal insufficiency that has not resolved to Grade ≤1 or patient is not stable on replacement therapy within 12 weeks;
- Grade 2 ocular event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 ocular event;

- Grade 3 dermatologic event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 4 dermatologic event, confirmed Stevens Johnson syndrome or toxic epidermal necrolysis;
- Any Grade 3 or 4 infusion-related reaction;
- Immune-mediated meningoencephalitis (any grade);
- Grade 3 or 4 amylase and/or lipase elevation or Grade 2 or 3 immune-mediated pancreatitis that has not resolved to Grade ≤1 within 12 weeks; or Grade 4 immune-mediated pancreatitis;
- Grade 2 immune-mediated neuropathy that has not resolved to Grade ≤1 within 12 weeks or Grade 2 facial paresis that has not resolved fully within 12 weeks; any Grade 3 or 4 immune-mediated neuropathy (including facial paresis); myasthenia gravis or Guillain-Barre syndrome (any grade); Grade 2 to 4 immune-mediated myelitis;
- Grade 2 to 4 immune-mediated myocarditis;
- Grade 2 to 4 immune-mediated pericardial disorders;
- Grade 2 or 3 hypophysitis that has not resolved to Grade ≤1 within 12 weeks, recurrent or any Grade 4 hypophysitis;
- Grade 2 renal event/nephritis that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 renal event/nephritis;
- Grade 2 or 3 immune-mediated myositis that has not resolved to Grade ≤1 within 12 weeks, recurrent or any Grade 4 myositis;
- Suspected HLH.

In all the above listed cases, resumption of atezolizumab may be considered for 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 investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed. In case of patients receiving steroids for management of immune-mediated adverse events, atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced/tapered to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed. For further details, including complete management guidelines for the above listed immune-mediated events, refer to the current Atezolizumab Investigator's Brochure.

DETAILED OVERVIEW OF THE 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 aetiology.

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.

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

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

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider *with*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.
- *Withhold* atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day *oral* prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. Resumption of

atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge 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.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Coronavirus disease 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Appendix 8: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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.

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

Event	Management
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 of 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

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 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 aetiologies 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]
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 aetiologies. 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, *initiate* empiric IV *corticosteroids* 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 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) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist for evaluation and 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
Hypothyroidism, Grade 1	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Hypothyroidism, Grade 2	• 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.
Hypothyroidism, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer *patient* to endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]

MRI = magnetic resonance imaging

[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.)

Hyperthyroidism, Grade 1	**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.
Hyperthyroidism, Grade 2	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer *patient* to 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

[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.)

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]
Hyperglycaemia, 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.
Hyperglycaemia, 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

[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.)

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

[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 the 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

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

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin,* B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on *immune-mediated* pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on *immune-mediated* myocarditis above).

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

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

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

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

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grade 2–4 ***or*** Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone *for 3–5 days* and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within *24* hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

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

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

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

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

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

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.
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. • 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.[e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • 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. • 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 Scale 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 the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

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

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

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

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

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

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the 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. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

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

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

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

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 aetiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in Table 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 aetiology. • 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 aetiology 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: – *Initial observation OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain.* – 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 *and proceed as per Guillain-Barré syndrome management.*
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone. • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider IV methylprednisolone 1 g/day for 3–5 days and consider other immunosuppressive agent.*

Event	Management

IVIG = intravenous immunoglobulin.

[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 neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to 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. • Initiate *non-opioid* treatment *(e.g., pregabalin, gabapentin, duloxetine) for pain.* • *Hospitalize patient.* – *Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone.* – *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage* as per institutional guidelines. • *Refer patient to neurologist.*

IVIG = intravenous immunoglobulin.

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 oedema. 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 aetiology, 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, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common aetiologies (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 aetiology, 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 *closely*, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • 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/*creatine phosphokinase*), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to

a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis *(see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).*

Patients with signs and symptoms of myositis, in the absence of an identified alternate aetiology, 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 ≤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 14 Management Guidelines for Immune-Mediated Myositis

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. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24–48 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.

Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab 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. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IVIG =intravenous immunoglobulin.

[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

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

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

Patients with suspected HLH should be diagnosed according to published diagnostic criteria by McClain and Eckstein (2018). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:

  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 52.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected *HLH* should be treated according to the guidelines provided in Table 15.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• 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.

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