Official Title: Interventional Platform Study Investigating The Impact Of Digital Health Solutions On Health Outcomes And Health-Care Resource Utilization In Participants Receiving Systemic Treatment In Clinical Practice (Origama)

NCT Number: NCT05694013

Document Date: Protocol Amendment Version 2: 23-May-2023

PROTOCOL

PROTOCOL TITLE:	**INTERVENTIONAL PLATFORM STUDY INVESTIGATING THE IMPACT OF DIGITAL HEALTH SOLUTIONS ON HEALTH OUTCOMES AND HEALTH-CARE RESOURCE UTILIZATION IN PARTICIPANTS RECEIVING SYSTEMIC TREATMENT IN CLINICAL PRACTICE (ORIGAMA)**
PROTOCOL NUMBER:	MO42720
VERSION NUMBER:	2
REGULATORY AGENCY IDENTIFIER NUMBERS:	EudraCT Number: 2021-001415-90 EU CT Number: 2023-504342-55-00 NCT Number: NCT05694013
INVESTIGATIONAL MEDICINAL PRODUCT:	Atezolizumab (RO5541267) (Cohort B)
SPONSOR/FUNDING SOURCE:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	See electronic date stamp on final page of this document.
1	8 March 2022

PROTOCOL AMENDMENT, VERSION 2

RATIONALE

Protocol MO42720 Version 2 has been amended to update it based on current experience with the trial, new advancements in the field, and feedback from the approval process, as well as to align with the new European CTR process. Changes to the protocol, along with a rationale for each change, are summarized below:

- The study has been registered at ClinicalTrials.gov. The registration number is NCT05694013 (global update).
- The study has been registered with the European Clinical Trials Information System (CTIS). The registration number is 2023-504342-55-00 (global update).
- The term 'flex care' has been corrected throughout to 'at-home treatment,' which is clearer (global update).
- The term 'participant(s)' has been corrected throughout to 'patient(s)' as appropriate (global update).
- It has been clarified that the Kaiku Health Digital Patient Monitoring (DPM) Solution used in the study is not considered an investigational medical device but rather a medical device as this device is CE marked in Europe and registered in Australia and used within its intended purpose (global update).
- The synopsis has been simplified to align with CTR, Sponsor processes, recommendations from TransCelerate and the Clinical electronic Structured Harmonised Protocol (CeSHarP) M11 (Section 1.1).
- A section describing duration of participation has been added to the synopsis to align with CTR requirements.
- Details on U.S. Food and Drug Administration (FDA) regulatory enforcement discretion, General Data Protection Regulation (GDPR) compliance in active European Union markets, and details on transfer of the Kaiku Health device legal manufacturer role to Elekta Solutions AB have been included/updated (Section 2.4).
- Background information on rHuPH20 (an excipient to Atezolizumab SC) has been added to the protocol and removed reference to the IB. Instead, the US package insert is referenced (Section 2.7).
- Study results from IMscin001 have been updated (Section 2.8).
- The platform nature of the trial has been detailed (Section 3).
- The exploratory efficacy objective "care team satisfaction with workflow efficiency" has been removed, as it will be addressed separately in a research project focusing on selected countries and clinics (Section 3.1.1.3).
- The exploratory endpoint for Cohort A "utilization (e.g., adherence) of Roche DPM Atezolizumab Module" has been extended with "and platform" to allow analysis of not only the Roche modules but also the DPM platform itself (Section 3.1.1.3).

- Safety related exploratory endpoints have been moved to safety endpoints, as requested by the Norwegian health authority (Section 3.1.2.4).
- A definition of the end of the study has been provided and the timing for closing each cohort has been clarified separately, as the cohorts are independent and expected to finish at different time points (Section 4.2).
- End of DPM provision has been clarified with the aim to provide DPM as soon as possible to patients on the treatment, and on safety follow-up, while taking operational complexities into consideration (Section 4.2.1 and 4.2.2).
- Cohort A inclusion criterion “Participant is systemic therapy naive (except for participants with EGFR mutant or ALK positive NSCLC who may have received prior systemic therapy with tyrosine kinase inhibitors as per the local approval)” has been removed as there should be no impact from previous treatments on DPM on patient reported symptom burden and other DPM related outcomes (Section 5.1.3.2).
- An inclusion criterion (Cohort B) has been included where the patients confirm to the investigator ensuring that their patient home is adequate to perform the at-home treatment visits, in accordance with European Medicines Agency (EMA) recommendation paper on decentralized elements in clinical trials released on 13 December 2022 (Section 5.1.3.3).
- The exclusion criteria from “participants currently participating in another interventional trial” has been updated to “participants currently enrolled in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study” to avoid ambiguous patient selection (Section 5.1.4.1).
- It has been clarified that the exclusion criteria “history of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death” is only applicable to only Cohort B (Section 5.1.4.3).
- The exclusion criteria of “uncontrolled tumor-related pain” has been updated; details on “uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures; history of leptomeningeal disease” have been removed as there will be no metastatic patients in Cohort B (Section 5.1.4.3).
- The medical term “Wegener granulomatosis” has been replaced by the term “granulomatosis with polyangiitis” to align with the updated preferred term in MedDRA (Section 5.1.4.3, Appendix 5).
- Details on discontinuation of Atezolizumab in patients under Cohorts A and B have been described. In the case of discontinuation, the DPM modules used in the study are no longer applicable and suitable for the patient. Therefore, patients will stop using DPM and all other study assessments. In Cohort A, patients will continue to report patient-reported outcomes until Week 24 (Sections 5.3.1.1.2, 5.3.1.2.6, and 5.6.1.1).
- The detail on collection of household income has been removed as this has been demonstrated to have minimal or no impact on DPM utilization (Section 5.5.2).

- Details on the collection of the estimated travel time from the patients' home to the study site have been included. The time required for the patient to travel to the study site might influence the patient's decision to receive the treatment at-home or at the study site (Section 5.5.2.1).
- The weight measurements on Day 1 of each cycle have been removed. Weight will only be measured during the hospital visits in Cohort B and not during the treatment at-home phase. The dosing of the study medication is not weight-dependent. Weight changes will be monitored during the disease control visits only as an indicator of potential side effects (Section 5.5.3).
- It has been clarified that laboratory samples will only be analyzed per standard of care (Section 5.5.7.2).
- The treatment at-home visit in Cohort B and the availability of the lab results for the treatment administration at-home have been clarified (Section 5.5.7.3).
- It has been explained that the samples collected during screening, treatment cycle 1–3 and disease control visits will be analyzed by the local laboratory and during the at-home treatment visits, samples will be analyzed by the central laboratory (Section 5.5.7.3 and Schedule of Activities).
- It has been clarified that the recall period used for the MD Anderson Symptom Inventory (MDASI) interference questionnaire is 7 days. This clarification was included as the pivotal literature referenced and summarized used the 24-hour recall period (Section 5.5.8.2).
- The text "in addition, 3 items from an MDASI tumor-specific module will allow patients to rate RCC and treatment-related symptoms (skin rash or change, sores in throat and mouth, and headache)" has been removed as the tumor-specific module for RCC is not included in the study (Section 5.5.8.2).
- The list of identified risks for Atezolizumab has been updated to include pericardial disorders, myelitis, and facial paresis (Sections 5.5.9.1, 6.2.1.1, and Appendix 7).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with Atezolizumab (Sections 5.5.9.1 and 6.2.1.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Sections 5.5.9.2 and 6.2.1.1).
- The requirement of patient initials for patients in Cohort B, in injection or infusion-related reaction (IRR) site reaction photography has been removed, as this is not required to capture with this kind of event and documentation (Section 5.5.9.2 and 6.2.2.4).
- It has been clarified that because the device is made as per CE mark, device medical complaints are no longer needed (Section 5.5.9.4).

- Personal identifiable information (i.e., name and telephone number) for the medical monitors from the protocol has been removed. Medical monitor contact information has been replaced with a sentence indicating that this information will be provided separately to the sites (title page, protocol amendment acceptance form, and Sections 5.5.9.4, and 6.2.4.1).
- [redacted]
- An email address has been included to report adverse device incidents to a generic inbox and providing more instructions regarding the requirements for reported information. (Section 6.1.3.4).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 9.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 10.6)
- Language has been clarified in Section 10.7 to indicate that any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.
- It has been specified that screening and enrollment in Cohort A can occur on the same day. The schedule of activities has been updated (Appendix 1).
- A time window of 72 hours to laboratory assessments has been added at Day 1 of Cycle 1 in Cohort A and B to prevent repeated laboratory tests (Appendix 1).
- The symptom of hypertension has been removed from Appendix 3. This symptom can only be reported by patients who regularly measure their blood pressure, which is not feasible in the study setting. Instead, patients can report symptoms associated with hypertension such as shortness of breath, chest pain, nausea and headaches.
- Appendix 5 has been revised to indicate that caution should be used when considering Atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
- Appendix 5 has been revised to include autoimmune myelitis.

- It has been clarified that in at-home treatment settings, emergency medical services are to be called immediately and the provided rescue medication (epinephrine) is to be used as applicable to stabilize the patient until emergency medical services arrive (Appendix 6) although it is already described under procedures of Appendix 6. In line with the current EAACI guidelines, it was decided to not provide the rescue medication kit drugs for the treatment of acute anaphylaxis, but rather to concentrate on Epinephrine, USP Auto-Injector 0.3 mg for IM injection. As per EMA recommendation, 2 of these will be provided to each patient throughout the at-home treatment phase, as a provision for the initial acute management of symptoms by a qualified healthcare provider, in the event of suspected anaphylaxis.
- The adverse event management guidelines have been updated to align Appendix 7 with the Atezolizumab Investigator's Brochure, Version 19 and associated Addenda 1 and 2.
- A comprehensive list of investigational medicinal products (IMPs), and non-IMPs has been included to align with CTR requirements (Appendix 8).
- Administrative changes:
  - The Australian Register of Therapeutic Goods (ARTG) number has been included for completeness, as Kaiku Health is already registered and had registration number in Australia (Section 6.1.1.1).
  - The reference for EAACI guidelines has been included: Anaphylaxis (References).
  - The time window has been clarified to complete questionnaires ($\pm$3 days) in Cohort A and B (Appendix 1, schedule of activities for Cohort A).
  - It has been clarified that the patients in Cohort B who stop receiving the at-home treatment may continue to receive the treatment during hospital visits as long as Atezolizumab SC is not discontinued (Appendix 1).
  - Socioeconomic status has been added to the schedules of activities for Cohorts A and B (Appendix 1), while it was already mentioned in the protocol body of Section 5.5.2.
  - A serology test has been added to the schedule of activities for Cohort B (Appendix 1, schedule of activities for Cohort B) while it was earlier mentioned in the protocol body of Section 5.5.7.3.
  - A 3–day window has been allowed for randomization in Cohort A and to provide more flexibility in site workflow (Appendix 1, schedule of activities for Cohort A).
  - The need for disease control visits has been specified in Cohort B only during the at-home treatment phase. It has also been clarified that this visit type takes place in the hospital (Appendix 1), while this was previously mentioned in the protocol body of Section 2.7, 4.1.2.
  - The at-home treatment cycle length for Cohort B has been clarified (Appendix 1, schedule of activities for Cohort B).

- Testing and documentation of programmed cell death-ligand 1 (PD-L1)-positivity status during screening assessment has been added to the schedule of activities (Appendix 1).
- An item, “Other symptoms” has been added to the symptom list in Appendix 3 to reflect actual software implementation. This allows patients to report any other symptom they experience that is not in the predefined symptom list.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**INTERVENTIONAL PLATFORM STUDY INVESTIGATING THE IMPACT OF DIGITAL HEALTH SOLUTIONS ON HEALTH OUTCOMES AND HEALTH-CARE RESOURCE UTILIZATION IN PARTICIPANTS RECEIVING SYSTEMIC TREATMENT IN CLINICAL PRACTICE (ORIGAMA)**
PROTOCOL NUMBER:	MO42720
VERSION NUMBER:	2
TEST COMPOUND:	Atezolizumab (RO5541267) (Cohort B)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

1. PROTOCOL SUMMARY

SYNOPSIS

PROTOCOL TITLE:	**INTERVENTIONAL PLATFORM STUDY INVESTIGATING THE IMPACT OF DIGITAL HEALTH SOLUTIONS ON HEALTH OUTCOMES AND HEALTH-CARE RESOURCE UTILIZATION IN PARTICIPANTS RECEIVING SYSTEMIC TREATMENT IN CLINICAL PRACTICE (ORIGAMA)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	EudraCT number: 2021-001415-90 EU CT Number: 2023-504342-55-00 NCT Number: NCT05694013

STUDY RATIONALE

This study will evaluate the impact of digital health solutions (DHS) on health outcomes and health-care resource utilization in people receiving systemic anti-cancer treatment (approved or non-approved) in clinical practice. DHS have the potential to improve clinical practice so that it is more data-driven and more personalized (Imison et al. 2016).

This study is designed to become a platform for the evaluation of an individual DHS in combination with a pre-specified drug treatment or group of treatments in one or more treatment settings, in separate cohorts. Initially, two cohorts will be opened (Cohorts A and B). *Cohorts may use the same software as a medical device, collect and analyze the same solution data (e.g., use and workflow efficiency), or use the same patient-reported outcome (PRO) measures.*

In Cohort A, the DHS “Roche Digital Patient Monitoring (DPM) Atezolizumab Module” will be assessed. “Roche DPM Atezolizumab Module” refers to the treatment-specific patient module, installed on a Digital Patient Monitoring solution. "Treatment" refers to the prescribed anti-cancer treatment regimen (i.e., Atezolizumab (intravenous [IV]) regimen or any new regimen thereafter) that participants are receiving.

In Cohort B, the combination of the DHS “Roche DPM Atezolizumab Module” and subcutaneous (SC) Atezolizumab administered in the at-home *treatment* setting will be explored. "Treatment" refers to Atezolizumab SC, administered in the hospital setting (Cycles 1–3) followed by the at-home setting (Cycles 4–16), if appropriate.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• Cohort A: To evaluate the efficacy of a locally approved anti-cancer regimen containing Atezolizumab (IV) and local standard of care (SOC) support plus the Roche DPM Atezolizumab Module compared to an anti-cancer regimen containing Atezolizumab (IV) with local SOC support only.	• Mean difference in change of Week 12 value from baseline of the patient-reported Total Symptom Interference Score from the MD Anderson Symptom Inventory (MDASI) Core Items
• Cohort B: To evaluate the feasibility of combining the Roche DPM Atezolizumab Module and Atezolizumab SC administered in the at-home treatment setting.	• At-home treatment adoption at Cycle 6
Secondary Objectives	**Corresponding Endpoints**
• Cohort A: To evaluate the efficacy of a locally approved anti-cancer regimen containing Atezolizumab (IV) and local standard of care (SOC) support plus the Roche DPM Atezolizumab Module compared to an anti-cancer regimen containing Atezolizumab (IV) with local SOC support only.	• Number of hospitalizations and number of cumulative days hospitalized due to serious adverse events (SAEs) • Unscheduled visits to the emergency room (ER) or clinic visits for symptom management • Incidence, nature, and severity of all anti-cancer treatment associated adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0. • Change from baseline in Global Health Status (GHS) score/Quality of Life (QoL) score from the European Organisation for Research and Treatment of Cancer (EORTC) Item Library 6 (IL6) GHS/QoL • Change from baseline in EuroQol EQ-5D-5L index-based and visual analogue scale (VAS) instrument • Change from baseline in the mean symptom severity score from the MDASI Core Items

OVERALL DESIGN AND STUDY POPULATION

This is an interventional, open-label, multi-country, platform study to investigate the impact of the Roche DPM Atezolizumab Module (installed on a DPM solution) on health outcomes in people prescribed a locally approved anti-cancer regimen containing Atezolizumab (IV) in the following indications:

- Metastatic non-small cell lung carcinoma (mNSCLC)
- Extensive-stage small-cell lung carcinoma (ES-SCLC)
- Advanced or unresectable hepatocellular carcinoma (HCC)

There will be two cohorts. The study will evaluate one DHS per cohort in combination with a pre-specified treatment or group of treatments in one or more treatment settings. In general, primary efficacy outcomes will be measured based on *patient*--reported outcomes. Initially, two cohorts testing the efficacy and safety of the Roche DPM Atezolizumab Module in combination with Atezolizumab IV (Cohort A) or the clinical utility of the Roche DPM Atezolizumab Module in combination with Atezolizumab SC in the at-home setting (Cohort B) will be opened. Additional cohorts will be added through future protocol amendments. Each cohort may have separate endpoints, screening, and treatment requirements. Cohorts within this study will run in parallel.

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

Phase:	Phase II/III	**Population Type:**	Adults
Control Method:	Patients receiving the same anti-cancer therapy and SOC support only	**Population Diagnosis or Condition:**	Histologically confirmed diagnosis via local labs for one of the following indications: • mNSCLC • ES-SCLC • HCC (Child Pugh A)
Interventional Model:	Parallel groups in Cohort A	**Population Age:**	≥ 18 years
Test Compound{s}:	Atezolizumab SC (RO5541267)	**Site Distribution:**	Multi-country
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization (Cohort A)
Number of Arms:	2 arms in Cohort A and 1 arm in Cohort B	**Number of Participants to Be Enrolled:**	400 in Cohort A [redacted] in Cohort B

ES-SCLC = extensive-stage small-cell lung carcinoma; HCC = hepatocellular carcinoma; mNSCLC = metastatic non-small cell lung cancer.

STUDY TREATMENT

The study treatment is detailed in the table below.

Population (as per local approval)	Atezolizumab anti-cancer therapy (regimens as per local approval)
mNSCLC	Atezolizumab 840 mg IV Q2W or 1200 mg Q3W or 1680 mg Q4W (until disease progression or unmanageable toxicity) monotherapy. Treatment beyond disease progression may be considered at the discretion of the physician.
mNSCLC (non-squamous)	Four to six 21-day cycles of Atezolizumab 1200 mg IV + chemotherapy (bevacizumab + carboplatin + paclitaxel, or carboplatin + nab-paclitaxel) induction therapy, followed by Atezolizumab 1200 mg Q3W + bevacizumab maintenance therapy (until disease progression or unmanageable toxicity). Treatment beyond disease progression with Atezolizumab monotherapy may be considered at the discretion of the physician.
ES-SCLC	Four 21-day cycles of Atezolizumab 1200mg IV + chemotherapy (carboplatin + etoposide) induction therapy, followed by Atezolizumab 840 mg IV Q2W or 1200 mg Q3W or 1680 mg Q4W maintenance therapy, including bevacizumab where locally approved (until disease progression or unmanageable toxicity). Treatment beyond disease progression may be considered at the discretion of the physician.
Advanced or unresectable HCC (Child Pugh A)	Atezolizumab 1200mg IV Q3W + bevacizumab 15 mg/kg IV Q3W (until loss of clinical benefit or unmanageable toxicity)[a]

ES-SCLC = extensive-stage small-cell lung carcinoma; HCC = hepatocellular carcinoma; mNSCLC = metastatic non-small cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks.

a If bevacizumab is discontinued due to toxicity, Atezolizumab regimen may continue until loss of clinical benefit or unmanageable toxicity.

DURATION OF PARTICIPATION

Based on a total recruitment duration of 16 months and a follow up of 12 months for all *patients*, unless they withdraw from the study sooner, the *time* from randomization of the first *patient* to the end of Cohort A, is expected to be approximately 28 months. *DPM provision for all patients will be discontinued 12 months after last patient is randomized.*

Based on a total recruitment duration of 16 months and a follow up of 15 months for all *patients*, unless they withdraw from the study sooner, the *time* from enrollment of the first *patient* to the end of Cohort B, is expected to be approximately 31 months. *DPM provision for each patient will be discontinued 3 months after the last dose of study treatment has been administered.*

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	adverse device effect
AFP	alpha-fetoprotein
ALK	anaplastic lymphoma kinase
ARTG	Australian Register of Therapeutic Goods
CIF	cumulative incidence function
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRS	cytokine-release syndrome
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DHS	Digital Health Solution
DPM	Digital Patient Monitoring
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	*European Medicines Agency*
EORTC	European Organisation for Research and Treatment of Cancer
EORTC OUT-PATSAT7	*EORTC satisfaction with out-patient cancer care*
ePRO	electronic *patient*-reported outcome
ER	emergency room
ESAB	*Elekta Solutions AB*
ES-SCLC	extensive-stage small-cell lung carcinoma
FDA	*(U.S.)* Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSCA	*field safety corrective action*
GDPR	General Data Protection Regulation
GHS	global health status
GMR	*geometric mean ratios*
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV/HCV	hepatitis B/C virus
HCC	hepatocellular carcinoma
HCP	healthcare professional

Abbreviation	Definition
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
HUS	hemolytic-uremic syndrome
IB	Investigator Brochure
IC	immune cells
IEC	Independent Ethics Committee
IL	Interleukin
IL6	item library 6
IMP	investigational medicinal product
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	injection or infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LFT	liver function test
MAS	macrophage activation syndrome
MDASI	MD Anderson Symptoms Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
(m)NSCLC	(metastatic) non-small cell lung carcinoma
MRI	*magnetic resonance imaging*
NCCN	*National Comprehensive Cancer Network*
NCI	National Cancer Institute
NIMP	*non-investigational medicinal product*
OS	overall survival
PD	progressive disease
PD-1	*programmed cell death-1*
PD-L1	programmed cell death-ligand 1
PFS	progression free survival
PK	*Pharmacokinetic*
popPK	*population PK*
PRO	*patient*-reported outcome
Q2W	*every 2 weeks*
Q3W	*every 3 weeks*
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase enzyme
SADE	serious adverse device effect

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	*Society for Immunotherapy of Cancer*
SmPC	Summary of Product Characteristics
SOC	standard of care
TNBC	triple-negative breast cancer
TTD	time to discontinuation
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
WTS	weighted toxicity score

2. BACKGROUND

2.1 DIGITAL HEALTH SOLUTIONS

Digital health solutions (DHS) use digital technology, including software and connectivity platforms, for health-related uses (FDA 2020). There is increasing interest in the use of technology-based digital health solutions to improve patient engagement, better inform disease diagnosis and drug treatment, and enhance clinical care inside or outside the clinic (EXPH 2018).

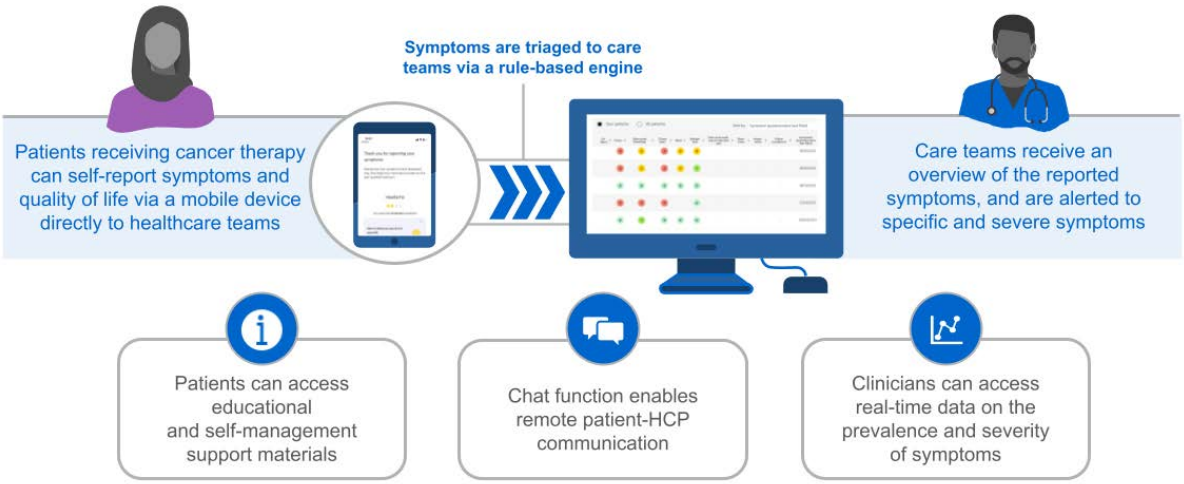
2.2 WEB-BASED, DIGITAL PATIENT MONITORING SYSTEMS

As time spans between clinic appointments for drug infusions and the availability of oral or subcutaneous drug formulations increase, there is an increasing need for remote monitoring of patients for symptoms and quality of life between clinic appointments (Aapro et al. 2020). Several web-based systems and apps have been developed to help monitor and manage people undergoing cancer treatments. These include features such as online symptom and quality of life reporting and monitoring (Absolom et al. 2021; Denis et al. 2017; Fjell et al. 2020), healthcare professional (HCP) patient online communication (Fann et al. 2017; Fjell et al. 2020) and education services (Fann et al. 2017; Fjell et al. 2020) (Figure 1). These can be accessed from web–enabled devices and have been shown to effectively prompt HCPs to more frequently monitor, and better manage patient-reported symptoms (Basch et al. 2016; Warrington et al. 2019; Denis et al. 2017; Fjell et al. 2020; Borosund et al. 2014; Fann et al. 2017). Most of these web-based solutions allow people to use their own electronic devices (such as computers, tablets, or mobile phones) to report in real-time and communicate with their HCPs (Warrington et al. 2019) (Figure 1).

Several solutions which combine all or selected features of those listed above have been investigated in clinical trials or introduced into clinical practice already (Warrington et al. 2019; Aapro et al. 2020). Besides enabling continuous tracking and aggregation of symptom information, such solutions have been shown to improve patient overall survival (OS), and duration of drug treatment (Basch et al. 2017; Basch et al. 2016), reduce the rate of severe or serious adverse events (Degenhardt et al. 2020; Mir et al. 2020), improve health-related quality of life (HRQoL) (Schmalz et al. 2020; Basch et al. 2016; Basch et al. 2017; Denis et al. 2017; Denis et al. 2019), reduce symptom severity or interference (Mooney et al. 2021; Rasschaert et al. 2021; Fjell et al. 2020; Kolb et al. 2018; Cleeland et al. 2011; Borosund et al. 2014), and depression or anxiety (Fann et al. 2017; Borosund et al. 2014; Maguire et al. 2021). Furthermore, these solutions have demonstrated health-economic benefits, including a reduction in hospital admission rates and unscheduled visits, increased use of ambulatory care, and a reduction in the need for patient phone calls and time for patient visits (Schmalz et al. 2020; Basch et al. 2016; Basch et al. 2017; Denis et al. 2017; Denis et al. 2019;

Pritchett et al. 2021; Mir et al. 2020; Mooney et al. 2021; Mooney et al. 2020; Hough et al. 2020; Hough et al. 2021).

Figure 1 Digital Patient Monitoring Solutions Enable Patients to Report Symptoms Systemically



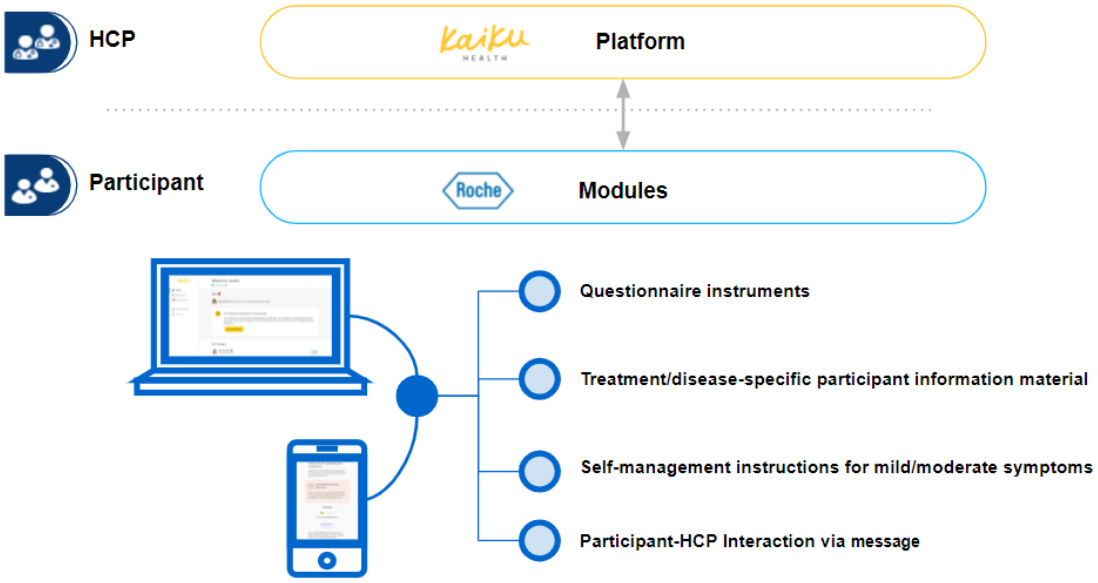
2.3 ROCHE DPM MODULE

The Roche Digital Patient Monitoring (DPM) Module is tailored to Roche requirements including but not limited to the *patient*-facing user interface, questionnaire instruments, and content (such as treatment/disease-specific *patient* information material and self-management instructions for mild/moderate symptoms), and algorithms for symptom alerting. It is mobile-enabled and accessible through a web browser or an app (with iOS or Android operating system) on internet capable devices such as personal computers (PCs), laptops, mobile phones, and tablets. In the module, *patients* can input data that is visible to care teams in real time (once the questionnaire has been submitted). *Patient*s can also communicate with care teams via message on the DPM platform.

In this protocol, "*patient*" refers to the individual receiving anti-cancer treatment who is enrolled in this study.

An overview of the Roche DPM Module is illustrated in Figure 2

Figure 2 Roche DPM Module Overview



2.3.1 Roche DPM Module Indications

A Roche DPM Module can cover several indications and treatments. However, only symptom questions or information relevant to the individual *patient's* disease and treatment will be displayed to the *patient*.

In Cohort A of this study, the Roche DPM Atezolizumab Module is used in *patients* with extensive-stage small-cell lung carcinoma (ES-SCLC); metastatic non-small cell lung carcinoma (mNSCLC); and advanced or unresectable hepatocellular carcinoma (HCC); who have not received prior anti-cancer systemic therapy. In Cohort B of this study, the Roche DPM Atezolizumab Module is used in participants with resected Stage IIB-IIIB (early-stage) NSCLC who have had a complete resection of NSCLC, are adequately recovered from surgery, and have completed up to four cycles of adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence.

2.3.2 Roche DPM Module Installation

The Roche DPM Module is hosted on the Kaiku Health DPM Solution but is technically separable from the Kaiku Health DPM Solution and could be integrated to other compatible DPM Solutions than the Kaiku Health DPM Solution after the study. During the study, centers will use the Roche DPM Modules installed on the Kaiku Health DPM Solution.

2.4 THE KAIKU HEALTH DPM SOLUTION

The Kaiku Health DPM Solution is a digital platform for symptom tracking and *patient*-reported outcomes monitoring. It has been developed to assist the care team in tracking and managing participant symptoms and triaging those symptoms based on

severity, as defined by a scoring algorithm that generates a single composite numerical grade for each *patient-reported outcome–Common Terminology Criteria for Adverse Events* (PRO-CTCAE) symptom (Basch et al. 2021). The solution can alert the HCP of new symptom events and facilitate triage by assisting with *patient* prioritization based on severity of reported symptoms. It can provide an overview of participants' symptom burden and interaction history. Further details on the Kaiku Health DPM Solution functionalities can be found in Section 5.3.1.1.

[redacted]

Indication for the Kaiku Health Platform

Kaiku Health is intended for all cancer diseases at all stages of treatment and follow-up.

Intended Use Statement for Kaiku Health Platform

- In the European Union: Kaiku Health is intended for use in cancer care and follow-up for non-urgent communication between an adult patient and a medical professional and for collecting patient-reported data, displaying and analysing clinical and patient-reported data, and instructing the patient. The data processed by Kaiku Health are intended to be used in supporting treatment decisions and in supporting diagnoses.

Kaiku Health has regulatory approval in, but not limited to, the following countries: the European Union, Australia, New Zealand, Switzerland, and United Kingdom, and can be used under enforcement discretion in the United States. In countries where Kaiku Health is approved, it should be used in line with the locally approved intended use statement.

2.5 BACKGROUND ON CANCERS, TREATMENT-RELATED SYMPTOMS, AND TREATMENT ADMINISTRATION

Cancer is a global public health issue and one of the leading causes of death globally (Global Burden of Disease Cancer Collaboration 2019; WHO 2020a; Bray et al. 2021). In 2020, there were an estimated 19.3 million new cancer cases and 10 million cancer-related deaths worldwide (WHO 2020b). The global incidence of new cases continues to rise, reflecting the ageing population as well as lifestyle changes that increase the prevalence of cancer risk factors (Warrington et al. 2019; Torre et al. 2016). The number of new cancer cases worldwide is expected to increase to 30.2 million in 2040 (WHO 2020b).

Early diagnosis and advances in cancer treatments have resulted in improved cancer survival rates (Arnold et al. 2019; Allemani et al. 2018). Individuals are now living for many years after cancer diagnosis and the number of cancer survivors is increasing (Alfano et al. 2018). However, treatment-related symptoms or adverse events experienced during treatment, as well as long-term consequences of anti-cancer treatment, are frequent and a common concern for people with cancer and HCPs and can cause increased risk of hospitalization and health care utilization (Rashid et al. 2015; George et al. 2021) and be a reason for early anti-cancer treatment discontinuation (Warrington et al. 2019; Nurgali et al. 2018). People living with cancer may experience acute and chronic effects due to treatment that can negatively impact their HRQoL and may even become life-threatening, with some individuals developing severe cases of neutropenia-related infection or other complications, or offsetting the improvement in outcomes seen with modern cancer treatments (Warrington et al. 2019; Bhattacharya et al. 2012; Gallegos-Kearin et al. 2018; Smith et al. 2021). A reduction of the adverse consequences of cancer treatment is therefore a priority for cancer research (Smith et al. 2021).

Symptom and adverse event monitoring and management by HCPs is an essential part of cancer care (Chindaprasirt et al. 2013) and earlier and better integrated cancer care was shown to improve outcomes (Temel et al. 2017). As stated in Section 2.2, digital patient monitoring and management of symptoms has been shown to positively impact outcomes and health care resource utilization (Schmalz et al. 2020; Basch et al. 2016; Basch et al. 2017; Denis et al. 2017; Denis et al. 2019; Pritchett et al. 2021; Mir et al. 2020; Mooney et al. 2021; Mooney et al. 2020; Hough et al. 2020; Hough et al. 2021).

Cancer treatment is traditionally provided in a hospital or oncology clinic setting and administered through intravenous (IV) infusion (Wardley et al. 2021). Treatment of people with cancer in these settings can be resource-intensive, time-consuming, and burdensome for those living with cancer, impacting HRQoL (Wardley et al. 2021; Aumann et al. 2015). *At-home treatment* describes care that is administered outside of the oncology ward, oncological outpatient clinic, or office-based oncologist setting. *At-home treatment* may take place in various settings, including the patient's home, primary

care, or community care, offering benefits for both people with cancer and hospitals. Programs that bring cancer treatment closer to the patient or provide care within the patient's home have been shown to improve quality of life, increase satisfaction with treatment and adherence, reduce costs and burden, and improve outcomes (Borras et al. 2001; Leff et al. 2005; Shepperd et al. 2009; Cryer et al. 2012; Mitchell. 2013; Cool et al. 2019). *At-home treatment* may also increase hospital capacity and save time for HCPs (De Cock et al. 2016).

2.6 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (Tecentriq®) is a fully humanized, engineered monoclonal antibody of IgG1 isotype that targets programmed cell death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T-cells. Therapeutic blockade of PD-L1 binding by Atezolizumab 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 Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T-cells.

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

Atezolizumab is approved as IV infusion for the treatment of urothelial carcinoma, Stage II to IIIA NSCLC (PD-L1 positive), mNSCLC, hepatocellular carcinoma (HCC), ES-SCLC, melanoma, and locally advanced unresectable or metastatic triple-negative breast cancer (mTNBC; PD-L1 positive). In Cohort A, an anti-cancer regimen containing Atezolizumab (IV) will be prescribed according to the local approval.

A formulation of Atezolizumab for SC administration is currently undergoing clinical evaluation in Study BP40657 (IMscin001) and Study MO43576 (IMscin002). Study BP40657 is a Phase Ib/III multicenter study investigating the pharmacokinetics, efficacy, and safety of SC administered Atezolizumab compared with Atezolizumab IV in *patients* with previously treated locally advanced or *m*NSCLC.

Sixty-seven patients were enrolled in Part 1: 13 patients in cohort 1, 15 in cohort 2, and 39 in cohort 3 (Felip et al. 2021). SC Atezolizumab 1800 mg every 3 weeks and 1200 mg every 2 weeks provided similar C_{trough} *and area under the curve (AUC) values in Cycle 1 to the corresponding IV Atezolizumab reference.* C_{trough} *values were 121 µg/mL in cohort 1 (1800 mg SC every 3 weeks, thigh), 83.2 µg/mL in cohort 2 (1200 mg SC every 2 weeks, thigh), and 97.3 µg/mL in cohort 3 (1800 mg SC every*

3 weeks, abdomen). Exposure following SC injection in the abdomen was lower (20%, 28%, and 27% for C_{trough}, maximum concentration, and area under the concentration-time curve from time 0 to day 21, respectively) than in the thigh.

Atezolizumab SC was well tolerated, and the safety profile was consistent with the known risks of Atezolizumab IV. Injection-site reactions were low grade and well tolerated. Seven of 11 patients experienced an injection site reaction in Cycle 1; six were Grade 1 and one was Grade 2 which resolved without sequelae.

Based on these results, a SC dose/regimen of 1875 mg q3w was selected for evaluation in Part 2 of the study (Dose confirming, Phase III, randomized). Part 2 will aim to confirm that this SC dose yields drug exposure that is comparable to that of IV Atezolizumab.

In IMscin001 Part 2 (randomized Phase III of the study), adults with previously treated locally advanced/metastatic NSCLC (no prior cancer immunotherapy) and ECOG PS 0 or 1 were randomized 2:1 to receive 2L Atezolizumab SC (1875 mg) or IV (1200 mg) every 3 weeks. Primary endpoints were non-inferiority for Cycle 1 observed serum C_{trough} and model-predicted AUC_{0-21} days; secondary endpoints were steady-state pharmacokinetics, safety, efficacy (PFS, ORR), patient-reported outcomes and immunogenicity.

There were 247 and 124 patients in the Atezolizumab SC and IV arms, respectively (median follow-up: 4.6 months; data cut-off: 26 April 2022). Median age was 64.0 years (range: 27–85), 69% were male and 74% had ECOG PS 1. The lower bounds of the 90% CI of the geometric mean ratios (GMRs) for C_{trough} (GMR 1.05 [90% CI: 0.88, 1.24]) and AUC (GMR 0.87 [90% CI: 0.83, 0.92]) were above the predefined non-inferiority margin of 0.8. Efficacy, immunogenicity, and safety were similar between arms (Burotto et al. 2022).

Atezolizumab SC demonstrated non-inferior exposure versus IV for both co-primary pharmacokinetic (PK) endpoints. Efficacy and safety were similar between arms and consistent with the known Atezolizumab IV profile. Atezolizumab immunogenicity was comparable between arms and within the historical range for Atezolizumab IV across indications. [redacted]

Study MO43576 is an ongoing Phase II randomized, multicenter, open-label, cross-over study evaluating *patient* and HCP reported preference for Atezolizumab SC compared with Atezolizumab IV in *patients* with NSCLC. In Cohort B of this study, all *patients* will receive Atezolizumab SC.

2.7 *BACKGROUND ON RECOMBINANT HUMAN HYALURONIDASE (RHUPH20)*

The feasibility and patient acceptability of SC administration of any drug are dependent on the volume of drug that must be administered. The recombinant human hyaluronidase enzyme (rHuPH20) (Hylenex® recombinant) is a hyaluronidase for human injection that has been developed by Halozyme Therapeutics, Inc., and is approved in the European Union and United States as a permeation enhancer to improve dispersion and absorption of SC formulations, enabling larger volumes to be administered without reduced tolerability and with improved patient acceptability. Hyaluronidase depolymerizes hyaluronan, a component of the SC matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of subcutaneously administered drugs to the systemic circulation. The hyaluronan in the SC space is restored within 24–48 hours. rHuPH20, a recombinant human molecule, has a higher purity and is associated with improved tolerability compared with the animal-derived enzyme (Hylenex recombinant U.S. Package Insert).

The safety and efficacy of hyaluronidase products have been widely established. The most significant safety risk identified is hypersensitivity/allergenicity, which is thought to be related to the lack of purity of the animal-derived preparations. This is not a safety concern for the human recombinant rHuPH20. The concentration of rHuPH20 is guided by data from a mini-pig study in which trastuzumab was administered subcutaneously. In the presence of either 2000 or 6000 U/mL of rHuPH20, there was a more rapid absorption of subcutaneously administered trastuzumab from rHuPH20-containing formulations, while the effect on the absorption rate of trastuzumab was comparable with both rHuPH20 concentrations. Therefore, the lower rHuPH20 concentration of 2000 U/mL was selected.

The highest total rHuPH20 dose administered in a clinical study was 96,000 U. This Phase I study investigated the SC injection of adalimumab with different rHuPH20 concentrations in healthy volunteers using different volumes of injection (2, 8, and 16 mL). All injections were well tolerated with no serious adverse events reported. Common injection-site reactions observed were erythema, ecchymosis, pain, and induration. All injection-site reactions, such as erythema, pain, and induration, were mild (98%) or moderate (2%).

To date, four monoclonal antibodies co-formulated with rHuPH20, are approved for SC therapy in oncology in the United States (PHESGO™ U.S. Package Insert; DARZALEX® U.S. Package Insert; HERCEPTIN HYLECTA™ U.S. Package Insert; RITUXAN HYCELA™ U.S. Package Insert) and four in the European Union (Darzalex® SmPC; Herceptin® SmPC; MabThera® SmPC; HyQvia® SmPC).

2.8 RATIONALE AND BENEFIT-RISK ASSESSMENT

Digital Patient Monitoring

DPM solutions have been shown to improve OS, with median OS increasing by 5 months in people with advanced cancers, and 9 months in people with lung cancer compared with standard care (Basch et al. 2017; Denis et al. 2019). Offering web-based support and education to people undergoing cancer treatment has also been shown to better help individuals self-manage their illness, enhance satisfaction with care, HRQoL, symptom severity or interference, and significantly improve psychosocial outcomes (Fjell et al. 2020; Borosund et al. 2014; Fann et al. 2017; Absolom et al. 2021; Mooney et al. 2021; Rasschaert et al. 2021; Fjell et al. 2020; Kolb et al. 2018; Cleeland et al. 2011; Borosund et al. 2014). Studies have shown significant improvements in depression, anxiety and physical wellbeing scores versus usual care (Borosund et al. 2014; Fann et al. 2017; Absolom et al. 2020).

Further studies suggest that DPM solutions may reduce the incidence of SAEs and thus the need for dose reductions (Degenhardt et al. 2020) and have also been associated with significantly higher relative dose intensity (Mir et al. 2020) and longer continued chemotherapy treatment than with usual care (Basch et al. 2017).

Identifying treatment-related symptoms promptly in people undergoing anti-cancer treatment can help HCPs with more effective management of treatment-related symptoms. Some web-based systems have been shown to enable care teams to intervene before symptoms worsen, leading to an improvement in symptom control (Mooney et al. 2021; Mooney et al. 2017; Berry et al. 2014; Fjell et al. 2020; Maguire et al. 2021; Kolb et al. 2018).

At-home Treatment

Anti-cancer therapy administered in the hospital setting is often burdensome to patients due to the need to travel and disruption of daily activities (Wardley et al. 2021; Aumann et al. 2015). The administration of anti-cancer therapy in a *at-home treatment*–setting (outside of the oncology ward, oncological outpatient clinic, or office-based oncologist setting), has been shown to reduce patient burden as well as improve quality of life, increase satisfaction with treatment and adherence, reduce costs, and improve outcomes (Borras et al. 2001; Leff et al. 2005; Shepperd et al. 2009; Cryer et al. 2012; Mitchell. 2013; Cool et al. 2021). The SC formulations of anti-cancer treatments may offer the preferred method of treatment administration in the *at-home treatment* setting due to quicker infusion times and easier administration.

Study MO42720

This study will evaluate a DHS in combination with a specified anti-cancer treatment in separate cohorts.

In Cohort A of this study, *patients* prescribed a locally approved anti-cancer regimen containing Atezolizumab (IV) in different indications will be enrolled and randomized to the Roche DPM Atezolizumab Module plus local standard of care (SOC) support or local SOC support only. Considering the high unmet medical need for the early detection and management of cancer treatment-related adverse events, the evidence presented above indicating that DPM solutions are safe and can improve outcomes and HRQoL in individuals with cancer, and robust procedures for risk minimization and mitigation employed in this study (see Section 6.1), the benefit–risk profile for Cohort A is considered to be favorable.

In Cohort B of this study, *patients* with early-stage NSCLC will receive three cycles of Atezolizumab SC administered in the hospital setting followed by up to 13 cycles of Atezolizumab SC administered in the at-home *treatment* setting, if appropriate, alongside the Roche DPM Atezolizumab Module.

The SC delivery of biotherapeutics is well-established as a route of administration that is effective and well-tolerated across many therapeutic areas (Collins et al. 2020). It can offer several advantages over IV administration, including the convenience of self-administration, improved *patient* experience, reduced treatment burden, and lower healthcare costs. Atezolizumab SC was shown to be well tolerated and exhibited a safety profile consistent with the known risks of Atezolizumab IV monotherapy in Study BP40657 (IMscin001). No new or significant safety concerns were identified. *Patient* and HCP reported preference for Atezolizumab SC compared with Atezolizumab IV is currently undergoing clinical evaluation in Study MO43576 (IMscin002).

There have been successful examples of drugs initially approved for IV administration that can now be safely administered as an SC injection in the *at-home treatment* setting by HCPs (Denys et al. 2020; Wolfromm et al. 2017; Walsh et al. 2007). Administration in the *at-home treatment* setting improves the quality of life and is more convenient, particularly for individuals who live far from a hospital or have difficulty travelling. In Cohort B of this study, the first three cycles of Atezolizumab SC will be administered in the hospital setting, as events that require immediate medical intervention, such as injection related reactions (IRRs), most commonly occur during the first three administrations. *Patients* may then receive up to 13 cycles of Atezolizumab SC administered in the at-home *treatment* setting. For *patients* who develop IRRs (or symptoms suggestive of IRR that require immediate medical intervention during infusion) during the first three cycles of Atezolizumab SC administration, all subsequent Atezolizumab SC administration will be done in the hospital setting only. For low grade (Grade 1–2) IRR events during the first three cycles, administration in the *at-home treatment* setting may be considered with premedication. Atezolizumab SC will be administered in the at-home *treatment* setting by a qualified mobile HCP with access to

adequate equipment to manage adverse events. The following additional risk mitigation strategies will be mandated by the protocol:

- Results from laboratory samples will be reviewed by the investigator prior to first Atezolizumab SC administration. From Cycle 4 onwards (treatment at home setting), laboratory samples will be collected *3 to 7 days prior* to Atezolizumab SC administration *so that results will be available by the time of treatment administration.*
- Laboratory samples will be collected by a qualified mobile HCP in the *at-home treatment* setting *or at the site as needed.*
- A phone or video call will be established between the qualified mobile HCP and the treating clinic HCPs during Atezolizumab SC administration in the at-home *treatment* setting.
- *Patients* will be prompted to complete symptom questionnaires via the Roche DPM Atezolizumab Module every 7 days as well as 24 hours after each Atezolizumab SC administration. The symptom questionnaire will include symptoms relevant to SC administration.
- *Patients* will visit the clinic HCP for a disease control and safety visit every three months during the *at-home* treatment period.

Considering the evidence that the safety profile of Atezolizumab SC is consistent with the known risks of Atezolizumab IV monotherapy, the high burden of hospital administration of anti-cancer treatment and the evidence presented above indicating that administration of anti-cancer treatment in the *at-home treatment* setting improves the quality of life and outcomes for people with cancer, and the risk minimization and mitigation strategies outlined above and in Section 6.2, the benefit–risk profile for Cohort B is considered to be favorable.

The overall risk for *patients* in all cohorts of this study receiving treatment with Atezolizumab (IV or SC) is expected to be low. Atezolizumab IV is an approved treatment for people with urothelial carcinoma, Stage II to IIIA NSCLC (PD-L1 positive), mNSCLC, HCC, ES-SCLC, melanoma, and locally advanced unresectable or metastatic triple-negative breast cancer (mTNBC; PD-L1 positive). The safety profile of Atezolizumab SC has been evaluated in Study BP40657 and was consistent with the known risks of Atezolizumab IV monotherapy.

This study is being conducted in compliance with ISO 14155 and incorporates a number of strategies to manage risk to the *patient*, including regular monitoring for *AEs*. Risk to the *patient* has been further minimized by completion of product testing for the Kaiku Health DPM Solution prior to its use in this study. A risk evaluation has been conducted by Kaiku Health, in accordance with ISO 14971. Identified residual risks and warnings presented to users of the Kaiku Health DPM Solution are outlined in Section 6.1.1.1.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade 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.

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 5.4).

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the impact of DHS on health outcomes and health-care resource utilization in people receiving systemic anti-cancer treatment (approved or non-approved) in clinical practice. DHS have the potential to improve clinical practice so that it is more data-driven and more personalized (Imison et al. 2016).

This study is designed to become a platform for the evaluation of an individual DHS in combination with a pre-specified drug treatment or group of treatments in one or more treatment settings, in separate cohorts. Initially, two cohorts will be opened (Cohorts A and B). *Cohorts may use the same software as a medical device, collect and analyze the same solution data (e.g., use and workflow efficiency), or use the same patient-reported outcome (PRO) measures.*

In Cohort A, the DHS "Roche DPM Atezolizumab Module" will be assessed. "Roche DPM Atezolizumab Module" refers to the treatment-specific *patient* module, installed on a Digital Patient Monitoring solution. "Treatment" refers to the prescribed anti-cancer treatment regimen (i.e., Atezolizumab IV regimen or any new regimen thereafter) that *patients* are receiving.

In Cohort B, the combination of the DHS "Roche DPM Atezolizumab Module" and Atezolizumab SC administered in the at-home *treatment* setting will be explored. "Treatment" refers to Atezolizumab SC, administered in the hospital setting (Cycles 1 to 3) followed by the at-home *treatment* setting (Cycles 4 to 16), if appropriate.

Specific objectives and corresponding endpoints for the study are outlined below.

3.1 EFFICACY AND SAFETY OBJECTIVES

3.1.1 Cohort A

3.1.1.1 Primary Efficacy Objective

Cohort A of this study will evaluate health outcomes in participants receiving a locally approved anti-cancer regimen containing Atezolizumab (IV) and local SOC support plus the Roche DPM Atezolizumab Module compared with participants receiving an anti-cancer regimen containing Atezolizumab (IV) with local SOC support only. The primary efficacy objective is to demonstrate superiority of the Roche DPM Atezolizumab Module on symptom interference on the basis of the following endpoint:

- Mean difference in change of Week 12 value from baseline of the participant-reported Total Symptom Interference Score from the MDASI Core Items

The primary comparison will be made regardless of whether $patients$ discontinue anti-cancer therapy or receive new anti-cancer therapy prior to Week 12, and in participants who have completed a minimum of two questionnaires only.

3.1.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for Cohort A of this study are to assess the impact of the Roche DPM Atezolizumab Module on:

- Number of hospitalizations and number of cumulative days hospitalized due to SAEs
- Unscheduled visits to the ER or clinic visits for symptom management
- Incidence, nature, and severity of all anti-cancer treatment associated AEs graded according to the (NCI-CTCAE v5.0) with additional analyses on:
  - Grade ≥ 3 AEs
  - SAEs
  - Selected immune-related AEs (pneumonitis, thyroid disorders, diarrhea or colitis, nephritis, rash, and hepatitis)
  - Weighted toxicity score (WTS) (Carbini et al. 2018)
  - Interruption, modification, or discontinuation of Atezolizumab regimen due to AEs
- Change from baseline in GHSscore/QoL score from the EORTC IL6 GHS/QoL
- Change from baseline in EuroQol EQ-5D-5L index-based and VAS instrument
- Change from baseline in the mean symptom severity score from the MDASI Core Items

3.1.1.3 Exploratory Efficacy Objectives

The exploratory objectives for Cohort A of this study are to explore the impact of the Roche DPM Atezolizumab Module on:

- $Patient$-reported satisfaction of healthcare treatment (EORTC OUT-PATSAT7 instrument)

- Time to discontinuation (TTD) of any prescribed anti-cancer treatment
- Time to clinical progression or death (PFS)
- Overall survival at 12 months
- Utilization of concomitant medication of special interest for management of AEs (e.g., steroids for irAEs; diarrhea medication; pain medication)
- Anti-cancer regimen drug dose intensity and exposure
- Utilization (e.g., adherence) of Roche DPM Atezolizumab Module *and platform*
- Predictive value of associating symptoms, laboratory test results, and AEs

3.1.1.4 Safety Objective

The safety objective for Cohort A of this study is to assess the safety of the Roche DPM Atezolizumab Module compared with local SOC support on the basis of the following endpoints:

- Incidence and severity of adverse events assessed as related to device use and adverse device effects
- Incidence, nature, and severity of anti-cancer treatment associated AEs as described in the secondary efficacy objectives (Section 3.1.1.2)

3.1.1.5 Biomarker Objective

There are no biomarker objectives in this study.

3.1.2 Cohort B

3.1.2.1 Primary Efficacy Objective

The primary efficacy objective in Cohort B is to evaluate the feasibility of combining the Roche DPM Atezolizumab Module and Atezolizumab SC administered in the *at-home treatment* setting on the basis of the following endpoint:

- *At-home treatment* adoption at Cycle 6

3.1.2.2 Secondary Efficacy Objectives

There are no secondary efficacy objectives for Cohort B in this study.

3.1.2.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives for Cohort B of this study are to explore the combined benefits of the Roche DPM Atezolizumab Module and Atezolizumab SC administered in the *at-home treatment* setting on:

- Utilization of Roche DPM Atezolizumab Module
- *At-home treatment* adherence at Cycles 9, 12, and 15
- Unscheduled visits to the ER or clinic for symptom management within one day of Atezolizumab SC administration
- Interruption, modification, or discontinuation of Atezolizumab due to AEs occurring within one day of Atezolizumab SC administration

- Time from first signs/symptoms to unscheduled clinic visit or hospitalization
- Reasons for not continuing in *at-home treatment* setting (questionnaire for *patients* / HCPs)
- Change from baseline in GHS/QoL from the EORTC IL6 GHS/QoL at Cycles 3, 6, 9, and 12
- Change from baseline in EuroQol EQ-5D-5L index-based and VAS instrument at Cycles 3, 6, 9, and 12
- Longitudinal description of symptom burden by MDASI at baseline and Cycles 3, 6, 9, and 12
- Characterize the safety of Atezolizumab SC administration in the hospital and *at-home treatment* settings on the basis of the incidence of adverse events (of any grade) within 1 day of Atezolizumab SC administration in a hospital or *at-home treatment* setting
- *Patient* acceptability of care and perception of safety culture in cancer care at Cycles 4, 6, and 8

3.1.2.4 Safety Objective

- *Number of hospitalizations within one day of Atezolizumab SC administration due to SAEs*
- *Incidence, nature, and severity of all Atezolizumab SC associated AEs graded according to the NCI-CTCAE v5.0 with additional analyses on:*
  - *Grade ≥ 3 AEs*
  - *SAEs*

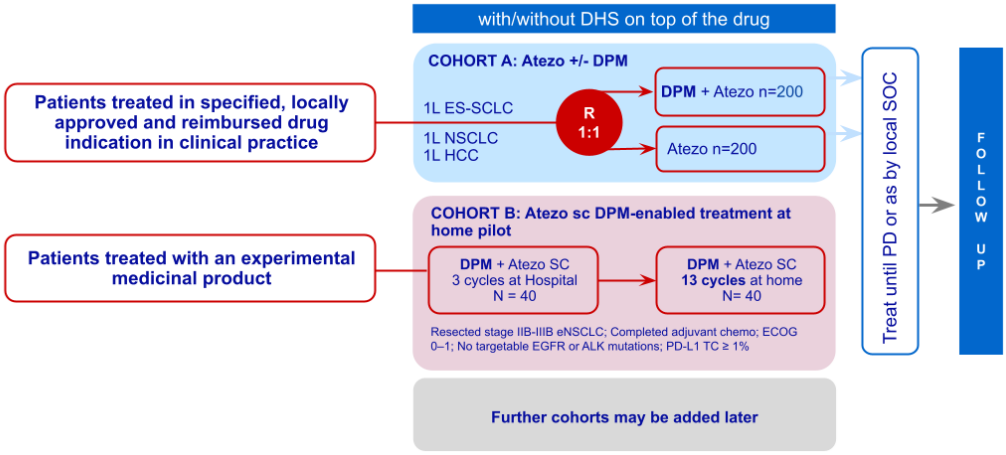
3.1.2.5 Biomarker Objective

There are no biomarker objectives in this study.

4. STUDY DESIGN

This is an interventional, open-label, multi-country, platform study. The study will evaluate one DHS per cohort in combination with a pre-specified treatment or group of treatments in one or more treatment settings. In general, primary efficacy outcomes will be measured based on *patient*-reported outcomes. Initially, two cohorts testing the efficacy and safety of the Roche DPM Atezolizumab Module in combination with Atezolizumab IV (Cohort A) or the clinical utility of the Roche DPM Atezolizumab Module in combination with Atezolizumab SC in the at-home *treatment* setting (Cohort B) will be opened (see Figure 3). Additional cohorts will be added through future protocol amendments. Each cohort may have separate endpoints, screening, and treatment requirements. Cohorts within this study will run in parallel. Figure 3 shows an overview of the study design.

Figure 3 Study Schema



Atezo = Atezolizumab; DHS = Digital Health Solution; DPM = Digital Patient Monitoring; ES–SCLC = extensive-stage small-cell lung carcinoma; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung carcinoma; PD = progressive disease; SOC = standard of care.

4.1 DESCRIPTION OF THE COHORTS

4.1.1 Cohort A

Cohort A will investigate the impact of the Roche DPM Atezolizumab Module (installed on the Kaiku Health DPM Solution; see Section 2.4) on health outcomes in people prescribed a locally approved anti-cancer regimen containing Atezolizumab (IV) in the following indications (Table 1):

- Metastatic non-small cell lung carcinoma
- Extensive-stage small-cell lung carcinoma
- Advanced or unresectable hepatocellular carcinoma

Each indication will make up no more than [redacted]% of the overall study population. *Patients* will be randomized into two arms, stratified by disease indication and baseline ECOG performance status; Roche DPM Atezolizumab Module plus local SOC support or local SOC support alone. *Patients* in the DPM arm will use the DPM solution to report symptoms, access educational materials, and communicate with care teams, as well as using their regular SOC methods of communication.

Table 1 Cohort A Population and Treatments

Population (as per local approval)	Atezolizumab anti-cancer therapy (regimens as per local approval)
mNSCLC	Atezolizumab 840 mg IV Q2W or 1200 mg Q3W or 1680 mg Q4W (until disease progression or unmanageable toxicity) monotherapy. Treatment beyond disease progression may be considered at the discretion of the physician.
mNSCLC (non-squamous)	Four to six 21-day cycles of Atezolizumab 1200 mg IV + chemotherapy (bevacizumab + carboplatin + paclitaxel, or carboplatin + nab-paclitaxel) induction therapy, followed by Atezolizumab 1200 mg Q3W + bevacizumab maintenance therapy (until disease progression or unmanageable toxicity). Treatment beyond disease progression with Atezolizumab monotherapy may be considered at the discretion of the physician.
ES-SCLC	Four 21-day cycles of Atezolizumab 1200mg IV + chemotherapy (carboplatin + etoposide) induction therapy, followed by Atezolizumab 840 mg IV Q2W or 1200 mg Q3W or 1680 mg Q4W maintenance therapy, including bevacizumab where locally approved (until disease progression or unmanageable toxicity). Treatment beyond disease progression may be considered at the discretion of the physician.
Advanced or unresectable HCC (Child Pugh A)	Atezolizumab 1200mg IV Q3W + bevacizumab 15 mg/kg IV Q3W (until loss of clinical benefit or unmanageable toxicity)[a]

ES-SCLC =extensive-stage small-cell lung carcinoma; HCC =hepatocellular carcinoma; mNSCLC =metastatic non-small cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks.

[a] If bevacizumab is discontinued due to toxicity, Atezolizumab regimen may continue until loss of clinical benefit or unmanageable toxicity.

Patients in Cohort A will be required to have a confirmed diagnosis from their treating physician for the relevant indication via local laboratory or radiological report in order to be enrolled into the study. There will be no central pathology laboratory or central radiology review or confirmation for study inclusion; however, if needed, sites might be asked to provide digital diagnostic images for research purposes, not decision making.

Patients that have been prescribed any of the cohort-specific anti-cancer systemic drug treatment in line with local approval and eligibility criteria, will be invited to discuss and sign informed consent (Table 1). Once all study inclusion criteria are satisfied, *patients* will be randomized 1:1 to receive either the Roche DPM Atezolizumab Module and local SOC support, or local SOC support only. Randomization will be stratified by disease

indication as outlined in Section 5.2.1 and by baseline ECOG performance status (0/1 vs. 2).

Upon randomization, *patients* will be asked to complete PRO assessment questionnaires before the first anti-cancer drug administration visit. All patients will complete PROs remotely on a regular basis throughout the study, as outlined in the schedule of activities

Patients in the DPM arm will receive access to the DPM solution and training on its use. *Patients* will return for visits as per their routine anti-cancer treatment administration schedule. Procedures and schedule for patients in the DPM arm will follow the usual SOC treatment schedule as detailed in the schedule of activities. No extra visits are mandated by this protocol. Additional clinic visits may occur at the discretion of both the care team and *patients*

Patients will continue to be assessed for the primary objective until Week 24 as per the schedule of *activities*, regardless of whether they have discontinued anti-cancer therapy or started a new line of therapy.

The primary reason for discontinuation of anti-cancer treatment, discontinuation of DPM, and withdrawal from the trial should be documented on the appropriate eCRF page. Safety data for the efficacy analyses and HRQoL data will continue to be collected for 90 days after the last dose of Atezolizumab and for 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow-up beyond this time point. Early discontinuation will be handled as described in the statistical section.

After 24 weeks, *patients* will continue to be followed as per the schedule of activities.

All *patient*s will be followed for OS until death, withdrawal of consent, loss-to-follow-up, 12 months after randomization, or end of study, whichever occurs earliest.

4.1.2 Cohort B

Cohort B will explore the benefits of the Roche DPM Atezolizumab Module (installed on the Kaiku Health DPM solution) in combination with Atezolizumab SC, administered by a HCP in the at-home treatment setting, on patient outcomes. All patients will use the DPM solution to report symptoms, access educational materials, and communicate with care teams, as well as using their regular SOC methods of communication. Patients with resected Stage IIB-IIIB (early-stage; per the UICC/AJCC staging system, 8th edition) NSCLC who have had a complete resection of NSCLC, are adequately recovered from surgery, and have completed up to four cycles of adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence will be

included. An overview of the study design is provided in Figure 3. The schedule of activities for Cohort B is provided in Appendix 1.

*Patient*s must have PD-L1-positive early-stage NSCLC to be enrolled in Cohort B of this study. *Patients* that do not have prior PD-L1 testing will be prospectively tested for PD–L1 expression by *an appropriate CE marked or* in-vitro diagnostics regulation *approved and as* per manufacturers recommendations and requirements at screening (see Sections 5.1.3 and 5.5.7 for more details).

Patients whose tumors have an EGFR -mutation or ALK rearrangement will be excluded from enrolment. *Patients* with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested at screening (see the specific exclusion criteria in Sections 5.1.4 and 5.5.7).

Eligibility for Cohort B of this study will be assessed within a 28-day screening period. *Patients* who do not meet the criteria for participation in Cohort B of this study (screen failure) may qualify for two rescreening opportunities (for a total of three screenings per *patient*) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1. Re screened *patients* must meet all eligibility criteria and re-sign the Informed Consent Form prior to re screening. The investigator will record reasons for screen failure in the screening log (see Section 5.5.1).

Patients will undergo a tumor assessment at baseline to confirm eligibility criteria. Subsequent tumor assessments will be conducted as per local SOC (see Section 5.5.5).

Patients will be asked to complete PRO assessment questionnaires before the first Atezolizumab SC administration visit. All *patients* will complete PROs remotely on a regular basis throughout the study, as outlined in the schedule of activities. All *patients* will receive access to the DPM solution and training on its use.

Patients will receive three cycles of Atezolizumab SC Q3W in the hospital setting before receiving up to 13 cycles of Atezolizumab SC Q3W in the *at-home treatment* setting. *Patients* will receive three cycles in the hospital setting, as events that require immediate medical intervention, such as infusion related reactions, most commonly occur during the first three administrations. For *patients* who develop IRRs (or symptoms suggestive of IRR that require immediate medical intervention during infusion) during the first three cycles of Atezolizumab SC administration, all subsequent Atezolizumab SC administration will be done in the hospital setting only. For low grade (Grade 1–2) IRR events during the first three cycles, administration in the *at-home treatment* setting may be considered with premedication. In the *at-home treatment* setting, Atezolizumab SC will be administered by a qualified mobile HCP with access to adequate equipment to manage AEs at the *patient's* home. During administration in the *at-home treatment* setting, a phone or video connection between the qualified mobile HCP and the treating clinic HCPs will be established. *Patients* who cannot continue administration of

Atezolizumab SC in the at-home *treatment* setting will be allowed to continue treatment in the hospital setting if there is clinical benefit, as judged by the investigator. Atezolizumab will be administered on Day 1 of each 21-day cycle. *Patients* will continue to receive Atezolizumab SC until Cycle 16.

Patients will undergo a post last treatment safety follow-up visit 28 days after completing study treatment and will undergo a safety follow-up telephone call 90 days after the last dose of study treatment.

Patients will be assessed for safety by regular evaluation of adverse events, vital signs, and routine clinical laboratory tests (hematology, blood chemistry), and by physical examinations. Adverse events will be graded according to the NCI CTCAE v5.0. In the *at-home treatment* setting, safety assessments will be carried out at every visit by the qualified mobile HCP in the *patient's* home *or by an HCP at the site based on investigator and patient decision*. *Patients* in the *at-home treatment* setting will also visit the clinic HCP every 3 months for a disease control and safety visit. *Patients* receiving treatment in the hospital setting will be assessed by the clinic HCP accordingly.

The primary reason for discontinuation of Atezolizumab SC, discontinuation of DPM, and withdrawal from the trial should be documented on the appropriate eCRF page. Early discontinuation will be handled as described in the statistical section.

4.1.3 Data Collection

Electronic Case Report Form (eCRF)

An eCRF will be used by care teams to collect and report patient clinical data across all arms at each scheduled anticancer drug administration visit. Data will be collected as per the schedule of activities and entered into the eCRF.

Electronic Patient-Reported Outcomes (ePROs)

HRQoL data measuring *patients'* ability to cope with disease and treatment will be collected via electronic PRO (ePRO) instrument questionnaires (as detailed in Section 5.5.8) and will be collected remotely as per indication every 6 weeks (± 3 days). *Patients* will complete the ePRO questionnaires through an app downloaded on an electronic device. A web link can be provided to capture PRO data if the *patient* does not have access to a suitable electronic device.

DPM solution

The DPM solution will be used to report symptoms and communicate via message with care teams. *Patients* will be required to report symptoms as they occur and at least every 7 days if not completed the DPM will send a reminder to *patients*. In addition, *patients* in Cohort B will be prompted to complete symptom questionnaires 24 hours after Atezolizumab SC administration. Data capturing use of the DPM solution by the *patient* or care teams is collected within the DPM. Additional qualitative data may also be collected via interviews with the *patients* and/or care teams.

4.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date of the last patient, last visit or when assessment occurs for the collection of the last data point for the last cohort, whichever occurs later. Any of the cohorts may close before the end of the entire study when all predefined treatment, follow-up, and data collection are completed for that cohort. In addition, the Sponsor may decide to terminate a cohort or the study at any time.

4.2.1 Cohort A

The end of the study for Cohort A is defined as the date at which the last data point required for statistical analysis is received from the last *patient*. Based on a total recruitment duration of 16 months and a follow up of 12 months for all *patients*, unless they withdraw from the study sooner, the *time* from randomization of the first *patient* to the end of Cohort A, is expected to be approximately 28 months. *DPM provision for all patients will be discontinued 12 months after last patient is randomized.*

4.2.2 Cohort B

The end of the study for Cohort B is defined as the date at which the last data point required for statistical analysis is received from the last *patient*. Based on a total recruitment duration of 16 months and a follow up of 15 months for all *patients*, unless they withdraw from the study sooner, the *time* from enrollment of the first *patient* to the end of Cohort B, is expected to be approximately 31 months. *DPM provision for each patient will be discontinued 3 months after the last dose of study treatment has been administered.*

4.3 RATIONALE FOR STUDY DESIGN

4.3.1 Cohort A

4.3.1.1 Rationale for Cohort A Population

Patients undergoing anti-cancer therapy typically experience unwanted symptoms, which they are often only able to report to their care teams at infrequent scheduled follow-up appointments. Use of DPM allows individuals to regularly self-report symptoms and HRQoL measures (via PRO), access support materials, and communicate with care teams at their convenience (Warrington et al. 2019). Use of DHS in *patients* with cancer has been shown to effectively prompt HCPs to more frequently monitor, and better manage symptoms - which in turn can improve outcomes and wellbeing (Basch et al. 2016; Warrington et al. 2019; Absolom et al. 2020; Denis et al. 2017; Fjell et al. 2020; Borosund et al. 2014; Fann et al. 2017).

DPM has been shown to improve OS, HRQoL (Basch et al. 2016; Denis et al. 2017; Denis et al. 2019), duration of treatment (Basch et al. 2016), and reduce the rate of severe or serious adverse events (Degenhardt et al. 2020; Mir et al. 2020), among other benefits. Furthermore, these DPM solutions have demonstrated health-economic benefits, including a reduction in hospital admission rates and unscheduled visits; and

the need for patient phone calls and time for patient visits (Schmalz et al. 2020; Basch et al. 2016; Denis et al. 2017; Denis et al. 2019).

As the described benefits of DPM appear to be independent of the tumor type, Cohort A of this study will include different tumors and tumor type will be included as a stratification factor. Only *patients* prescribed anti-cancer treatment with an Atezolizumab (IV) regimen will be included, to prevent the need for another stratification factor, which would require an increased cohort size.

4.3.1.2 Rationale for Cohort A Procedures and Schedule

Cohort A aims to demonstrate that use of the Roche DPM Atezolizumab Module will result in a lower MDASI Total Symptom Interference Score in *patients* undergoing anti-cancer treatment with an Atezolizumab (IV) regimen compared with SOC support. A lower score indicates a reduction in symptom interference for *patient*s.

All *patients* will complete MDASI at baseline, every 6 weeks until Week 24, and at the 90-day follow-up telephone call to determine the Symptom Interference Score change of Week 12 value from baseline. *Patients* will also be followed the efficacy safety endpoints for 90 days after the last dose of Atezolizumab and for 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow-up beyond this time point.

The time point Week 12 was chosen based on evidence on symptom burden or interference improvements or stabilization reported for DPM solutions in other clinical trials (Mooney et al. 2021; Rasschaert et al. 2021; Fjell et al. 2020; Kolb et al. 2018), median duration of first-line treatment with an Atezolizumab regimen of 3–7 months in clinical trials, and expected adherence to PRO-CTCAE reporting over time (Basch et al. 2020). We will validate the adherence for PRO-CTCAE reporting in the Roche DPM Atezolizumab Module for the time point Week 12 in a Roche real-world scientific research project (KAISER).

Patients randomized to the DPM arm will use the Roche DPM Atezolizumab Module for the duration of the study and can continue using it until 3 months after their last Atezolizumab dose, if they feel it is beneficial to their care and if their care team supports use of the DPM solution.

4.3.1.3 Rationale for Choice of Cohort A Control Group

In order to study the impact of DPM, anti-cancer treatments need to be consistent across both arms. Therefore, the control group consists of *patients* receiving the same anti-cancer therapy and SOC support only.

4.3.1.4 Rationale for Cohort A Biomarker Assessments

Not applicable.

4.3.1.5 Rationale for Cohort A Non-Standard Clinical Outcome Assessments

Not applicable.

4.3.2 Cohort B

4.3.2.1 Rationale for Atezolizumab SC Dose and Schedule

Atezolizumab SC will be administered at a fixed dose of 1875 mg every 3 weeks (Q3W) (1875 mg on Day 1 of each 21-day cycle) into the thigh. This dose and administration site was chosen based on the results of Study BP40657 (IMscin001). In Part 1 of Study BP40657, Atezolizumab SC co-mix (an SC formulation of Atezolizumab for co-mix with rHuPH20, manually mixed at the local pharmacy), given at a dose of 1800 mg Q3W in the thigh, provided similar observed Cycle 1 C_{trough} and $AUC_{0-21\ d}$ values as Atezolizumab given at a dose of 1200 mg IV Q3W in Phase III study GO28915 (OAK) (observed Cycle 1 C_{trough} [CV %]: 121.1 μg/mL [42.8%] and 76.0 μg/mL [53.9%], respectively; Cycle 1 $AUC_{0-21\ d}$: 3868 μg•day/mL [38.6%] (observed) and 2978 μg•day/mL [26.1%] [model-predicted], respectively).

Atezolizumab pharmacokinetic (PK) data after both SC and IV administrations from Part 1 of Study BP40657 were modeled using a population PK (popPK) approach. A higher bioavailability was estimated for administration in the thigh (82.9%) compared with in the abdomen (71.1%), with an inter individual variability of 124%. Using the popPK model, simulations of the proposed Phase III study in Part 2 indicated that a SC dose of 1875 mg Q3W given in the thigh had a $>$99% probability of providing comparable PK exposures to Atezolizumab IV 1200 mg Q3W, in terms of Cycle 1 and steady state C_{trough} and $AUC_{0-21\ d}$.

Overall, Atezolizumab administered subcutaneously in Study BP40657 was well tolerated and exhibited a safety profile consistent with the known risks of Atezolizumab IV monotherapy. No new or significant safety concerns were identified. Refer to the Atezolizumab Investigator's Brochure for additional information.

4.3.2.2 Rationale for Cohort B Population

Patients in Cohort B will have early-stage NSCLC that is PD-L1 positive. All *patients* in Cohort B will be treated with Atezolizumab SC. Atezolizumab IV is currently FDA-approved as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq$ 1% of tumor cells based on the results of the Phase III Study GO29527 (IMpower010) (TECENTRIQ® U.S. Package Insert). The SC formulation of Atezolizumab is currently undergoing clinical evaluation in *patients* with previously treated locally advanced or metastatic NSCLC in Study BP40657 (IMscin001) and in early- and late-stage NSCLC in Study MO43576 (IMscin002).

4.3.2.3 Rationale for Cohort B Procedures and Schedule

Cohort B aims to be a pilot for investigating the feasibility of Atezolizumab SC administered in the at-home *treatment* setting combined with the Roche DPM Atezolizumab Module. The procedures and schedules within this cohort have been designed to support *patient* safety monitoring. Details of the criteria for administration in the *at-home treatment* setting and risk mitigation strategies mandated by this protocol are outlined in Section 2.7. Objectives are described in Section 3.1.2.

All *patient*s in Cohort B will use the Roche DPM Atezolizumab Module for the duration of the study and can continue using it until 3 months after their last Atezolizumab dose, if they feel it is beneficial to their care and if their care team supports use of the DPM solution.

4.3.2.4 Rationale for Choice of Cohort B Control Group

Not applicable.

4.3.2.5 Rationale for Cohort B Biomarker Assessments

Not applicable.

4.3.2.6 Rationale for Cohort B Non-Standard Clinical Outcome Assessment

Not applicable.

5. MATERIALS AND METHODS

5.1 PARTICIPANTS

5.1.1 Cohort A

Approximately 400 participants with the following indications will be enrolled in Cohort A of this study (see Table 1 for more details):

- mNSCLC
- ES-SCLC
- HCC

Each indication will make up no more than [redacted]% of the overall study population. Treatment per indication must be locally approved in each country taking part in the study and reimbursed. Absence of local reimbursement does not preclude participant enrollment. Treatment regimens will be as per local clinical practice and independent of participation in this study. Atezolizumab (IV) anti-cancer treatment regimen will not be provided as part of the study.

5.1.2 Cohort B

Approximately [redacted] participants with early-stage NSCLC will be enrolled in Cohort B of this study. The investigational medicinal product (IMP) for Cohort B is Atezolizumab SC. IMP will be supplied by the Sponsor.

5.1.3 Inclusion Criteria

Participants must meet the following criteria for study entry:

5.1.3.1 All Participants

- Participant is aged ≥ 18 years at time of signing Informed Consent Form.
- Participant has signed an Informed Consent Form according to local regulations.
- Be able to comply with the study protocol, according to investigator's judgement.
- Participant has an email address, access to an internet-capable device (smartphone, tablet, or PC), and access to an internet connection.

5.1.3.2 Cohort A

- Participants must have a histologically confirmed diagnosis via local laboratories, except where alternative means for diagnosis is established (e.g., contrast enhanced imaging with or without alpha-fetoprotein [AFP] for HCC, or cytologically for lung cancer), for one of the following indications for which an Atezolizumab (IV) regimen is locally approved (see Table 1):
  - mNSCLC
  - ES-SCLC
  - HCC (Child Pugh A)
- Participant is prescribed an Atezolizumab (IV) regimen and this decision must be made and documented prior to signing the *Informed Consent Form* and must follow local clinical practice, according to the Investigator's judgement within the constraints of the local approval
- ECOG Performance Status of 0, 1, or 2 (Appendix 2)
- Life expectancy ≥ 12 weeks

5.1.3.3 Cohort B

- *Participants must confirm adequacy of their home to conduct trial related procedures at-home.*
- Participants must have a complete resection of a histologically or cytologically confirmed Stage IIB-IIIB (T3-N2) NSCLC (per the UICC/AJCC staging system, 8th edition; Detterbeck et al. 2018)

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. For a right thoracotomy, sampling is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. Levels 10 and 11 are required irrespective of tumor laterality.

- PD-L1 positive as documented through local testing performed per manufacturer's recommendations and requirements of a representative tumor tissue specimen. *An appropriate CE marked or In-Vitro Diagnostics Device approved test should be used for local testing of PD-L1.*
- Participants must have completed adjuvant chemotherapy at least 4 weeks and up to 12 weeks prior to randomization and must be adequately recovered from chemotherapy treatment
- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L ($\geq$ 1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L ($\geq$ 500/μL)
  - Platelet count $\geq 100 \times 10^9$/L ($\geq$ 100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L ($\geq$ 9 g/dL)

    Participants may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

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

    Participants with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Participants with known Gilbert disease: total bilirubin $\leq 3 \times$ ULN
  - Creatinine clearance $\geq$45 mL/min (calculated through use of the Cockcroft-Gault formula)
  - Albumin $\geq$25 g/L ($\geq$ 2.5 g/dL)
  - For participants not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN
- For participants receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening, with the following exception: participants with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/µL, and have an undetectable viral load
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative hepatitis B surface antibody (HBsAb) at screening or positive HBsAb test at screening accompanied by either of the following:
  - Negative total hepatitis B core antibody (HBcAb)
  - Positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

The HBV DNA test must be performed for participants who have a negative HBsAg test, a negative HBsAb test, and a positive total HBcAb test.

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

  The HCV RNA test must be performed for participants who have a positive HCV antibody test.

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

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the final dose of Atezolizumab.

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

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

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

5.1.4 Exclusion Criteria

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

5.1.4.1 All Participants

- Participants with any physical or cognitive condition that, according to clinical judgement, would prevent the participant from using the DHS (e.g., dementia, hepatic encephalopathy)
- Participants not proficient with any of the available DHS language translations or with psychiatric/neurologic disorders or any condition that may impact the participant's ability to use the DPM solution
- *Participants currently enrolled in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study*

5.1.4.2 Cohort A

- Concomitant anti-cancer therapy at the time of starting Atezolizumab (IV) regimen on the index date which is not part of a locally approved combination therapy with Atezolizumab as per SmPC or local regulatory documents
- Participants not receiving Atezolizumab, but an Atezolizumab biosimilar or non-comparable biologic
- Participants currently using another DPM or ePRO solution for symptom management and/or reporting

5.1.4.3 Cohort B

- Participants known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene

  Participants with unknown EGFR or ALK mutational status whose tumor may harbor a sensitizing EGFR mutation (i.e., participants with non-squamous histology (including those with a mixed histology that includes any non-squamous component), and without any other known driver mutation) will be required to be tested at screening. Participants with tumors of squamous histology who have an unknown EGFR or ALK mutational status will not be required to be tested at screening.

  EGFR and/or ALK will be assessed locally. EGFR status must be performed on tissue using a test that detects mutations in exons 18–21. The assays must be a Health Authority approved test (i.e., adhering to local drug/device regulations) and performed per manufacturer's recommendations and requirements.

- *History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.*
- Uncontrolled tumor-related pain

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

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium > ULN)

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis *with polyangiitis*, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 5 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

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

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could impact participant safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

Participants receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease (COPD) exacerbation) are eligible for the study.

- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the participant at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during Atezolizumab treatment or within 5 months after the final dose of Atezolizumab
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Participants who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  - Participants who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the Atezolizumab formulation
- Pregnancy or breastfeeding, or intending to become pregnant during study treatment or within 5 months after the final dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20

- Pathology (e.g., lower extremity edema, cellulitis, lymphatic disorder or prior surgery, preexisting pain syndrome, previous lymph node dissection, etc.) that could interfere with any protocol-specified outcome assessment
- 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 randomization
- Participants currently using another DPM or ePRO solution for symptom management and/or reporting

5.2 METHOD OF INTERVENTION ASSIGNMENT AND BLINDING

5.2.1 Study Arm Assignment

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

5.2.1.1 Cohort A

A total of 400 evaluable *patients* will be randomized to one of two study arms:

- DPM arm (Roche DPM Atezolizumab Module plus local SOC support and a locally approved anti-cancer regimen containing Atezolizumab [IV])
- Comparator arm (local SOC support and a locally approved anti-cancer regimen containing Atezolizumab [IV] only)

Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each study arm. Randomization will be stratified according to the following criteria:

- Disease indication (Table 1)
- Baseline ECOG performance status (0/1 vs. 2)

Patients in Cohort A will receive anti-cancer treatment as per their local SOC and the eligibility criteria.

5.2.1.2 Cohort B

Cohort B of this study is an open-label, single-arm cohort that will enroll approximately [redacted] *patients*.

5.2.2 Blinding

This section is not applicable – this study is not blinded.

5.3 STUDY INTERVENTION AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

5.3.1 Study Treatment

5.3.1.1 Cohort A (Atezolizumab IV)

5.3.1.1.1 Atezolizumab IV Dosage, Administration, and Compliance

Patients with any of the indications listed in Section 5.1 will receive a locally approved anti-cancer regimen containing Atezolizumab (IV) and local SOC support plus the Roche DPM Module, or a locally approved anti-cancer regimen containing Atezolizumab (IV) and local SOC support only. The Atezolizumab (IV) anti-cancer treatment regimens for *patients* in both arms of Cohort A are summarized in Table 1. The anti-cancer treatment schedule for all *patients* in Cohort A will follow local SOC practices for each indication. Details are listed in Appendix 1. Details on anti-cancer treatment administration (e.g., frequency and timing) should be noted on the eCRF.

5.3.1.1.2 *Discontinuation of Atezolizumab IV*

Patients who discontinue Atezolizumab IV based treatment or switch to an Atezolizumab biosimilar or non-comparable biologic will have the post-last treatment safety follow-up visit. Patients access to Kaiku will be deactivated 90 days after the final Atezolizumab dose. The collection of MDASI, HRQoL. EORTC IL6, GHS/QoL, EQ-5D-5L and EORTC OUT-PATSAT7 will continue up until Week 24. After Week 24 the patient will discontinue from the study.

5.3.1.2 Cohort B (Atezolizumab SC)

Patients with resected early NSCLC will receive Atezolizumab SC plus the Roche DPM Module. After completion of three cycles of Atezolizumab SC in the hospital setting, eligible *patients* will receive up to 13 cycles of Atezolizumab SC in the at-home *treatment* setting (see Section 2.7 for criteria for administration in the *at-home treatment* setting and the qualified mobile HCP instruction manual for instructions on administration in the *at-home treatment* setting). *Patients* who cannot continue administration of Atezolizumab SC in the at-home *treatment* setting for any reason will be allowed to continue treatment in the hospital setting if there is clinical benefit, as judged by the investigator.

The *medical* device for Cohort B is the Roche DPM Atezolizumab Module (5.3.2.1). The IMP for Cohort B is Atezolizumab SC (Appendix 8 identifies all investigational and non-investigational medicinal products for this study). IMP will be supplied by the Sponsor. Anaphylaxis medications (Section 5.3.1.2.3) *are* regarded as non-investigational medicinal products (NIMPs). NIMPs will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements for any on site administration *(Appendix 8 identifies all investigational and non-investigational medicinal products for this study).*

5.3.1.2.1 Atezolizumab SC Formulation and Packaging

Atezolizumab SC will be provided as a sterile liquid at a concentration of 125 mg/mL. rHuPH20 will be co-formulated with Atezolizumab in the Atezolizumab SC formulation at a concentration of 2000 U/mL.

For information on the formulation and handling of Atezolizumab SC, see the pharmacy manual.

5.3.1.2.2 Atezolizumab SC Dosage, Administration, and Compliance

Atezolizumab (1875 mg) SC injections will be administered subcutaneously by a HCP in the anterior thigh region per the instructions outlined in Table 2.

The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. In all cases, start and stop times of the SC injection should be captured.

No premedication will be allowed for the first dose of Atezolizumab SC. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. Injection sites will be digitally photographed after a SC injection if a severe adverse reaction at the injection site is observed.

In case a *patient* develops toxicity that is linked to the treatment with Atezolizumab SC, further continuation of treatment is not recommended. Refer to Appendix 7 for further guidance on Atezolizumab toxicity management.

Atezolizumab SC must always be administered by a HCP with access to adequate equipment to manage AEs. The first three cycles of Atezolizumab SC will be administered in the hospital setting. *Patients* may then receive up to 13 cycles of Atezolizumab SC in the at-home *treatment* setting administered by a qualified mobile HCP (see qualified mobile HCP instruction manual for instructions on administration in the *at-home treatment* setting). During administration in the *at-home treatment* setting, a phone or video call will be established between the qualified mobile HCP and the treating clinic HCPs. For *patients* who develop IRRs (or symptoms suggestive of IRR that require immediate medical intervention during infusion) during the first three cycles of Atezolizumab SC administration, all subsequent Atezolizumab SC administration will be done in the hospital setting only. For low grade (Grade 1–2) IRR events during the first three cycles, administration in the *at-home treatment* setting may be considered with premedication.

For anaphylaxis precautions, see Appendix 6.

Table 2 Administration of First and Subsequent Atezolizumab SC Injections

First and Subsequent SC Injections
• No premedication is permitted prior to the **first** SC injection. • For subsequent SC injections, if the *patient* experienced an injection-related reaction with any previous injection, premedication with antihistamines, antipyretic medications, and/or analgesics may be administered at the discretion of the investigator. • Vital signs should be measured as described in Section 5.5.4. • *Patients* should be informed about the possibility of delayed post-injection symptoms and instructed to contact their study physician if they develop such symptoms

PK = pharmacokinetic.

5.3.1.2.3 Anaphylaxis Medication

The Sponsor will provide anaphylaxis kits for use in the at-home treatment setting to be used by the HCP in the event of a severe hypersensitivity reaction during or after administration of Atezolizumab SC.

These kits must be available before the first administration of Atezolizumab SC in the *at-home treatment setting*. Additional kits will be provided if kits expire, are damaged or are used during the study.

Anaphylaxis kits will contain *two* Epinephrine USP Auto-Injectors 0.3 mg for IM injection *(Muraro et al. 2022)*.

5.3.1.2.4 Investigational Medicinal Product Handling and Accountability

The IMP required for completion of Cohort B of this study (Atezolizumab SC) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or qualified mobile HCP]) 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 IMP 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 IMP received and that any discrepancies have been reported and resolved before use of the IMP. All IMP 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 Cohort B of this study may receive IMP, and only authorized staff may supply or administer IMP.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMP 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

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

5.3.1.2.5 Continued Access to Atezolizumab SC

The Sponsor will offer continued access to Roche IMP (Atezolizumab SC) 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 Roche IMP (Atezolizumab SC) 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 Roche IMP 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 Roche IMP (Atezolizumab SC) after completing the study if any of the following conditions are met:

- The Roche IMP 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 the IMP or data suggest that the IMP is not effective for NSCLC.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for NSCLC.
- Provision of the Roche IMP 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

5.3.1.2.6 *Discontinuation of Atezolizumab SC*

Patients that discontinue Atezolizumab SC treatment for any reason will have the post-last treatment safety follow-up visit and discontinue the study. Patient access to Kaiku will be deactivated 90 days after last Atezolizumab dose.

5.3.2 Medical Device

5.3.2.1 The Roche DPM Atezolizumab Module on the Kaiku Health DPM Solution (Cohorts A and B)

The Roche DPM Atezolizumab Module on the Kaiku Health DPM Solution is intended for informing treatment management decisions and is accessible through internet capable devices. It aims to facilitate non-urgent communication, including sharing of *patient*-reported data between *patient* and care team. It should be used by treated *patients* and their care teams in accordance with the training provided and as indicated in the user guide.

For the purposes of this study, the Roche DPM Atezolizumab Module on the Kaiku Health DPM Solution will be used for *patient* symptom reporting and non-emergency *patient*-care team communication only. *The care team includes nurses and physicians from the patient's study site. The care team triages according to local practice.*

Patients are able to report symptoms at pre-specified time points as well as when they happen, and notifications will be sent to care teams based on the severity of the symptom as reported by the patient. An algorithm will be used to generate a single composite numerical grade for each PRO-CTCAE symptom, to categorize symptoms by severity (Basch et al. 2021) and send notifications to care teams. The adverse event severity classification is independent of the algorithm symptom severity classification. The symptom severity classification generated by the scoring algorithm should not be used to determine the CTCAE grade of any AEs as determined by the investigator. Following submission of a symptom report, notifications are sent to the care team to help prioritize review and management of *patient*-reported symptoms. Notifications are classified into categories, as detailed in the Kaiku Health DPM Solution care team user interface section below. For selected mild or moderate symptoms, self-management instructions will be issued to *patients* in the DPM solution. For any symptom reported as severe, the participant is urged to contact the care team immediately.

This solution features two interfaces as outlined below:

Roche DPM Atezolizumab Module Participant User Interface

The participant user interface is accessible through internet capable devices such as PCs, laptops, mobile phones, or tablets. Patients will be able to report their symptoms

spontaneously, when they happen, and will also be prompted to complete symptom data via an internet browser-based or app-based online questionnaire every 7 days. In addition, *patients* in Cohort B will be prompted to complete symptom questionnaires 24 hours after Atezolizumab SC administration. *Patients* will receive an email when there is a new questionnaire to be completed. If a *patient* has not completed that questionnaire, reminders will be sent more often during the first week and then less frequently. If a participant is using the DPM solution through the app downloaded on their mobile phone or tablet, they may opt to receive push notifications instead of emails. Partially completed symptom questionnaires are saved as drafts. Every *patient* can view their own symptom information provided in a dashboard at any time. *Patient* cannot edit symptom reports once they have been sent. *Patients* can send messages to their care team at any time.

Patients should not obtain advice or help from others that may influence their assessment of symptoms (e.g., family members or friends) when completing the instruments beyond general help on device use.

Patient-reported symptom data are processed and the care team notified as described above. Based on populated symptoms, the user interface provides participants with feedback depending on the symptom severity - for selected mild to moderate symptoms the *patient* receives anti-cancer treatment regimen/disease-tailored educational materials (e.g., symptom severity assessment and self-management instructions).

As part of the introduction to the DPM solution, participants will be educated to call the emergency services or visit the nearest hospital when experiencing a severe symptom or other emergency.

Kaiku Health DPM Solution Care Team User Interface

The Kaiku Health web application has its own dedicated user interface for care team users that is designed to support clinical decision making. It enables care teams to track *patient-reported* symptoms between the clinic appointments, and triage participant information received. *Patient* data is available in real-time and automatically analyzed to generate notifications for new events and highlight severe symptom reports. Notifications are classified into the following three urgency categories based on evaluation of the scoring algorithm severity classification as well as the change of symptom severity grade relative to baseline:

- Alert: Symptom report contains a symptom of Grade 3 that was not included in the baseline report or a change of Grades ≥ 2 in any symptom
- Warning: Symptom report contains a change from Grade 1 to Grade 2 in any symptom
- Info: Symptom report contains a change from Grade 0 to Grade 1 in any symptom or contains a symptom that was reported as Grade 3 in the baseline report

Relevant care team members receive daily digest emails about new activity of the *patients* in their care. If a *patient* reports a symptom triggering a notification in the "Alert" category, a separate email is sent to the relevant care team members within approximately 15 minutes after receiving the *patients'* report.

In the care team DPM web app, care team members can assign incoming notifications to themselves or another member of the care team. Within approximately 15 minutes of assigning the *patient* report to a member of the care team, the member of the care team receives an email notifying them of the assignment. Symptom reports are only visible to the care team once the *patient* has sent the report. Members of the care team are not able to edit the symptom report.

Linked to the *patient* interface, the care team can exchange messages with *patients*.

The care team dashboard provides an overview of *patients'* activities including symptom questionnaire input and care team-*patient* interaction. The individual *patient* level decision support dashboard allows monitoring of disease progression and insights into *patient* history.

It is expected that care teams review the system for new data on a daily basis on weekdays, depending on the number of ongoing participants in the DPM arm.

Regulatory classification, data privacy, and technical requirements

Kaiku Health is compliant with industry regulations and is a CE-marked Class IIa medical device in the European Union, and is fully GDPR compliant. Data that will be shared between Kaiku Health and the Sponsor will be outlined in the data management plan.

Kaiku Health is compatible with most web browsers. The newest versions of Mozilla Firefox, Google Chrome, Microsoft Edge or Apple Safari are recommended for use. The basic usage of Kaiku Health does not require the installation of any plug-ins or extensions. For *patient* users, the mobile application is available for iOS (v 11.0 and later) and Android (v 5.0 and later).

Patients can use the Kaiku Health DPM Solution with either a native iOS or Android application and the web application. HCPs should use the web-based version of the platform only.

For detailed specifications on the Roche DPM Atezolizumab Module see the technical documentation.

5.3.2.1.1 Roche DPM Atezolizumab Module Schedule, Administration, and Compliance

The DPM solution allows *patients* to:

- report on their health and wellbeing using *a* predefined *list of symptoms (including free text for other symptoms),* as defined *for the respective indication of the* Roche DPM Atezolizumab Module *(Appendix 3)*,
- receive reminders, notifications and instructions related to reporting the predefined metrics,
- send encrypted messages and attachments to the care team.

Patients in Cohort A randomized to the DPM arm and all *patients* in Cohort B will undergo initial training by HCPs on the use of the DPM solution at the study baseline visit. *Patients* will then be able to use the Roche DPM Atezolizumab Module to report their symptoms as they arise and will receive reminders to do so at least every 7 days. In addition, *patients* in Cohort B will be prompted to complete symptom questionnaires 24 hours after Atezolizumab SC administration.

5.3.2.1.2 Roche DPM Atezolizumab Module Access, Handling, and Accountability

The Roche DPM Module *and access to the Kaiku Health DPM Platform* required for completion of this study will be provided by the Sponsor.

Only *patients* enrolled in the study and assigned to use the DPM may receive and use the Roche DPM Modules, and only authorized staff may provide access and training to the applicable *patients*.

Patients will provide their own internet-capable device and internet connection required to securely access the DPM solution.

5.3.2.1.3 Continued Access to the DPM Solution

For *patients* who wish to continue using the DPM, continued access will be available.

5.3.2.2 Comparator Arm for Cohort A - Anti-cancer Regimen Containing Atezolizumab (IV) and Local Standard of Care Support Only

Patients in the comparator arm for Cohort A of this study will receive a locally approved anti-cancer regimen containing Atezolizumab (IV) (see Section 5.3.1.1) and local SOC support only. *Patients* randomized to this arm will not receive access to the Roche DPM Atezolizumab Module on the Kaiku Health DPM Solution. The randomization of *patients* to this arm will not result in any changes to their current treatment plan. Symptom reporting for *patients* in the comparator arm will be done according to routine clinical practice. *Patients* will complete activities as per the schedule of *activities* specified in Appendix 1

and will receive supporting information and communication options as per local and individual site standards. *Patients* will complete a minimum number of PRO questionnaires to collect data for the study endpoints. This will occur outside of the DPM solution.

5.4 CONCOMITANT THERAPY

Concomitant therapy consists of any intervention (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to the protocol-accepted SOC systemic anti-cancer therapy from 7 days prior to initiation of study procedures to the final survival follow-up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, as required.

5.4.1 Concomitant Therapy for Cohort A

5.4.1.1 Permitted Therapy

In general, investigators should manage a participant's care with supportive therapies as clinically indicated, per local standard practice.

Participants in Cohort A are permitted to use the following therapies during the study:

- Palliative radiotherapy

5.4.1.2 Prohibited Therapy

There are no concomitant therapies that are prohibited in Cohort A of this study. The local approval for the Atezolizumab (IV) regimen must be followed.

The investigator should contact the Medical Monitor if questions arise regarding potential prohibited therapies.

5.4.2 Concomitant Therapy for Cohort B

5.4.2.1 Permitted Therapy

Participants in Cohort B are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 5.1.3)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live attenuated vaccines are not permitted (see Section 5.4.2.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for COPD or asthma (e.g.,10mg QD, prednisone or equivalent)

- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent Atezolizumab administrations only, at the discretion of the investigator.

In general, investigators should manage a $patient's$ care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 5.4.2.2 and 5.4.2.3) as clinically indicated, per local standard practice. $Patients$ who experience administration-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious administration-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 6).

5.4.2.2 Cautionary Therapy

5.4.2.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with Atezolizumab therapy (refer to Appendix 7 for details).

5.4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 5.4.2.3) may be used during the study at the discretion of the investigator.

5.4.2.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 5.1.4), and during study treatment, until disease progression is documented and the *patient* has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 5.4.2.1 for details).
- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during Atezolizumab treatment, and for 5 months after the final dose of Atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, *interferon* (IFNs) and *interleukin-2* (IL-2)) 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.

5.4.3 Additional Restrictions

This section is not applicable.

5.5 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 of the study intervention throughout the study.

For *patients* in Cohort B during the *at-home* treatment period, certain study assessments may be performed by a qualified mobile HCP at the *patients* home, to improve access and convenience for *patients* in the study. The Sponsor will select a healthcare company that will be responsible for providing qualified mobile HCP services for participating sites (the qualified mobile HCP vendor). The qualified mobile HCP vendor is responsible for ensuring that all qualified mobile HCPs are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. The qualified mobile HCP network will communicate with the participant and the participant's site. Qualified mobile HCP visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the qualified mobile HCP. The schedule of activities (See Appendix 1) will specify the assessments that may be performed by a qualified mobile HCP.

5.5.1 Informed Consent Forms and Screening Log (All Cohorts)

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

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

5.5.2 Medical History, Baseline Conditions, Concomitant Medication, Demographic Data, and Socioeconomic Status Data (All Cohorts)

Medical history, including clinically significant diseases, 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 participant within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

For Cohort A, participant evaluation prior to the decision to prescribe an Atezolizumab (IV) regimen will be considered part of the medical history. The date that Atezolizumab (IV) regimen was prescribed must be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (where allowed by local regulations).

Socioeconomic status data will be collected, including highest educational degree *and* occupation.

5.5.2.1 *Cohort B*

For patients in cohort B, the time required to travel from the patients' home to the study site will be collected as estimated by the patient.

5.5.3 Physical Examinations (All Cohorts)

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

Limited, symptom-directed physical examinations should be performed at specified post-baseline 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.

In Cohort B, limited, symptom-directed physical examinations may be performed by a qualified mobile HCP during treatment administration visits in the at-home *treatment setting*.

Height and weight will be recorded at screening. Weight *will* only *be recorded during visits in the hospital at the treatment phase* or whenever, the investigator considers there is a substantial change from baseline.

5.5.4 Vital Signs

5.5.4.1 All Cohorts

Vital signs will be carried out as per local SOC. Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the *patient* is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

5.5.4.2 Cohort B

Vital sign measurement may be performed by a qualified mobile HCP.

Vital signs should be measured within 60 minutes prior to each Atezolizumab injection, at 30 (±10) minutes after the injection, and as clinically indicated. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities.

5.5.5 Tumor and Response Evaluations (Cohort B)

Patients in Cohort B will undergo tumor assessments at screening to confirm eligibility criteria.

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, so long as they meet criteria outlined below.

During study treatment, *patients* will undergo regular tumor assessments as per local SOC. Disease progression or loss of clinical benefit as determined by the investigator should be recorded on the eCRF.

5.5.5.1 Radiographic Assessments (Cohort B)

Screening assessments must include CT scans with contrast or *magnetic resonance imaging (*MRI*)* scans of the chest, abdomen, pelvis, and brain. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in *patients* with impaired renal clearance), a non-contrast CT scan

of the chest may be performed and MRI scans of the abdomen, pelvis, and brain should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all *patients* (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease may be used.

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

5.5.6 Biomarkers

This section is not applicable.

5.5.7 Laboratory and Other Biological Samples

5.5.7.1 All Cohorts

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR, aPTT, and *prothrombin time (*PT*)*
- Thyroid function testing: thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4
- Urinalysis (pH, specific gravity, glucose, protein, ketones, blood*); dipstick permitted.*

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

Data arising from sample analysis, will be subject to the confidentiality standards described in Section 9.4.

5.5.7.2 Cohort A

Laboratory samples (see Section 5.5.7.1) will be collected to assess the predictive value of associated symptoms, laboratory test results, and AEs. It is expected that at every visit (scheduled or unscheduled) where AEs are reported, a corresponding laboratory sample (e.g., blood, urine) is taken and analyzed according to local SOC for management of the respective AE and results documented in the eCRF.

Laboratory samples collected as per Cohort A schedule of activities and SOC are analyzed according to local SOC. Therefore, not all of the analytes mentioned in Section 4.5.7.1 will be collected at all visits and samples can be taken prior to treatment administration.

5.5.7.3 Cohort B

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis *during screening, treatment Cycle 1–3 and disease control visits as applicable per schedule of activities*:

- HIV serology
- HBV serology: HBsAg, HBsAb, and total HBcAb for all *patients*; HBV DNA for *patients* with negative HBsAg and HBsAb tests and a positive total HBcAb test
- HCV serology: HCV antibody for all *patients*; HCV RNA for *patients* with a positive HCV antibody test
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine (or serum, if urine is not feasible) tests will be performed at specified subsequent visits. 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).
- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 expression and EGFR/ALK mutation status
- *Hematology, chemistry, coagulation, thyroid function testing, urinalysis, and pregnancy test*

In the treatment at-home period, samples for the below laboratory tests will be collected by a qualified mobile HCP within 3 to 7 days prior to treatment administration and

sent to the central laboratory for analysis. This is not required if there are valid local laboratory results available for that time window:

- *Hematology, chemistry, thyroid function testing, and pregnancy test (urine dipstick taken at the day of drug administration, before drug administration)*

Central laboratory results will be shared with the investigator prior to each planned drug administration at-home.

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report.

5.5.8 Clinical Outcome Assessments (All Cohorts)

Patient-reported outcome instruments will be completed to assess the benefit of the DPM solution.

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

- MDASI (Cohorts A and B)
- EORTC IL6 GHS/QoL (Cohorts A and B)
- EQ-5D-5L (Cohorts A and B)
- EORTC OUT-PATSAT7 (Cohort A)
- PRO-CTCAE (for participants using the DPM only) (Cohorts A and B)
- Participant acceptability questionnaire (Cohort B)

MDASI, EORTC IL6 GHS/QoL, and EQ-5D-5L will be used to assess patient-reported HRQoL, EORTC OUT-PATSAT7 will be used to assess *patient* satisfaction with out-patient cancer care, and PRO-CTCAE will be used to assess *patient*-reported symptoms in *patients* using the DPM. The participant acceptability questionnaire will be used to assess *patient* satisfaction with various aspects of the at-home *treatment* setting as well as *patient* perception of safety culture.

5.5.8.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at-home or at the clinic at specified time points during the study (see schedule of activities). At the clinic or at-home, MDASI, EORTC IL6 GHS/QoL, EQ-5D-5L, and EORTC OUT-PATSAT7 will be administered before the *patient* receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of anti-cancer treatment, unless otherwise specified. The participant acceptability questionnaire will be administered following treatment administration per the schedule of activities.

PRO instruments, translated into the local language as appropriate, will be completed through use of an ePRO app downloaded on the *patient's* own electronic device. The ePRO app will be independent of the DPM solution. The ePRO app will enable the appropriate instruments to be administered in the correct order at each specified time point. The link to download the app and instructions for completing the instruments electronically will be provided by the site staff. If the *patient* does not have access to a device capable of installing the app, a web link for the electronic completion of PROs may be provided. In the event that a *patient* does not have access to their own device at site visits, the site can provide an electronic device for the completion of PRO instruments. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Patients should be given the following instructions for completing PRO instruments at-home:

- *Patients* should complete the instruments in a quiet area with minimal distractions and disruptions.
- *Patients* should answer questions to the best of their ability; there are no right or wrong answers.
- *Patients* should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits and visits conducted by a qualified mobile HCP (Cohort B only), PRO instruments should be administered as outlined below:

- *Patients*' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be ~15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- *Patients* should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- *Patients* should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

5.5.8.2 Description of Clinical Outcome Assessment Instruments

MD Anderson Symptom Inventory (MDASI) (Cohorts A and B)

The MDASI is a cancer-related, multisymptomatic, validated, reliable self-report questionnaire for clinical and research use (Cleeland et al. 2000). It consists of 19 items over two scales that assess symptom severity and symptom interference with different aspects of a $patient's$ life. For 13 items (pertaining to pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sadness, vomiting, and numbness or tingling), $patients$ rate how severe the symptoms were when “at their worst” in the last $7\ days$. For 6 items, $patients$ rate how much the symptoms have interfered with six areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last $7\ days$. The MDASI items are rated from 0–10, with 0 indicating that the symptom is either not present or does not interfere with the $patient's$ activities and 10 indicating that the symptom is “as bad as you can imagine” or “interfered completely” with the participant's life. The MDASI takes approximately 5 minutes to complete.

EORTC Item Library 6 Global Health Status/Quality of Life (IL6 GHS/QoL from EORTC QLQ-C30) (Cohorts A and B)

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; Cocks et al. 2011). It consists of 30 questions that assess five aspects of $patient$ functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), GHS and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." EORTC QLQ–C30 module takes approximately 10 minutes to complete. The EORTC IL6 GHS/QoL consists of only the GHS and QoL items from the EORTC QLQ-C30 and will be used for this study. The EORTC IL6 GHS/QoL takes approximately 1 minute to complete.

EQ-5D-5L (Cohorts A and B)

The EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L), is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the $patient's$ current health status. Published weighting systems allow for creation of a single composite score of the $patient$'s health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

EORTC Satisfaction with Out-Patient Cancer Care (EORTC OUT-PATSAT7) (Cohort A)

EORTC OUT-PATSAT7 is a 7-item complementary module from PATSAT-33, a core questionnaire to assess *patient* satisfaction with cancer care. OUT-PATSAT7 specifically assesses aspects of ambulatory care: care convenience (3 items), transition (3 items) and care continuity (1 item). Items are assessed on a 5-point Likert scale ranging from Poor to Excellent for the most recent experience of care received by the *patient* (Brédart et al. 2018). Higher score indicates greater satisfaction with care.

PRO-CTCAE (Cohorts A and B)

The PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 *patient*-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of symptoms deemed most applicable to the current treatments has been selected for this study (see Appendix 3). Symptoms have been selected on the basis of expected symptoms due to underlying disease in the *patient* population or known Atezolizumab adverse drug reactions. Clinical care relevance of the selected symptoms has been reviewed, amended and confirmed by HCPs, *patients,* and *patient* representatives with relevant disease and treatment expertise.

Participant Acceptability Questionnaire (Cohort B)

The participant acceptability questionnaire will be used to assess convenience and *patient* satisfaction with the at-home *treatment* setting as well as *patients'* perception of safety. The questions are rated on a 4-points Likert scale ranging from strongly disagree to strongly agree. Concepts related to acceptability include *patient* preference of different locations for the administration of Atezolizumab SC treatment (Appendix 4).

5.5.9 Anti-cancer Treatment Associated Adverse Events

Anti-cancer treatment associated adverse events will be collected as part of the secondary efficacy objectives for Cohort A. Text on the assessment of safety of the DPM solution as part of the safety analyses is provided in Section 6.1.

5.5.9.1 Safety Plan

Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome,

myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 7 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for Atezolizumab.

Management of *Patients* Who Experience Adverse Events

Treatment Interruption or Discontinuation

Interruption or discontinuation of the anti-cancer regimen containing Atezolizumab (IV) should be done according to local approval and local SOC practices.

Management Guidelines

Management of *patients* who experience adverse events should be done according to the Atezolizumab local approval and local SOC practices.

5.5.9.2 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 5.5.9.4.

Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- 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 intervention (e.g., screening invasive procedures such as biopsies)

Serious Adverse Events *(Immediately Reportable to the Sponsor)*

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization
- 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 participant 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); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.9.4 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.9.4 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.5.9.3)

- Suspected transmission of an infectious agent by an anti-cancer 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 participant exposed to a medicinal product. This term applies only when a contamination of the anti-cancer treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade $\geq$2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

Adverse Events for Exploratory Research

For the purposes of the study objectives, additional laboratory data will be collected for the following selected adverse events:

- Pneumonitis
- Thyroid disorders
- Diarrhea or colitis
- Nephritis
- Rash
- Hepatitis

Injection-Site Reactions (Atezo SC)

With SC administration, local reactions at site of injection (erythema, pruritus, edema, rash, and pain) may occur. In case of severe injection-site reactions, unscheduled photographs will be taken. Photographs should include a label showing the subject's identification number, date and time of calendar date, and a centimeter ruler to provide scale. Efforts will be made to standardize the photography with regard to parameters such as angle, light, distance from body, and settings.

5.5.9.3 Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all events (see Section 5.5.9.2 for definitions) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this Section 5.5.9.3 and in Sections 5.5.9.4–5.5.9.7. The investigator is also responsible for reporting medical device complaints (see Section 6.1).

For each event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of anti-cancer 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 5.5.9.4 for instructions for reporting serious adverse events).

After initiation of anti-cancer treatment, all adverse events will be reported until 90 days after the last dose of Atezolizumab and for 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow-up beyond this time point.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.5.9.6.

Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time points. 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?"

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 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 participants 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 5.5.9.4 for reporting instructions), per the definition of serious adverse event in Section 5.5.9.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.5.9.4 for reporting instructions), per the definition of serious adverse event in Section 5.5.9.2.

Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the anti-cancer treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of anti-cancer treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of anti-cancer treatment, or reintroduction of anti-cancer treatment (as applicable)
- Known association of the event with anti-cancer treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant 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 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by anti-cancer 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 anti-cancer treatment, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to anti-cancer treatment; and/or the adverse event abates or resolves upon discontinuation of anti-cancer treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than anti-cancer 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 anti-cancer treatment (e.g., cancer diagnosed 2 days after first dose of anti-cancer treatment).

Procedures for Recording Adverse Events

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

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

Infusion-Related Reactions and Cytokine Release Syndrome

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

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

If a *patient* experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event 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 7.

Diagnosis versus Signs and Symptoms

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

Adverse Events That Are Secondary to Other Events

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

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

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

Persistent or Recurrent Adverse Events

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

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.5.9.4 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ 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 5.5.9.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.5.9.4).

Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.5.9.3) that are attributed by the

investigator solely to progression of cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to anti-cancer treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.5.9.4).

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.5.9.6.

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").

Lack of Efficacy or Worsening of Cancer

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non-small cell lung carcinoma, extensive-stage small-cell lung carcinoma, or hepatocellular carcinoma"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on investigator assessment according to local standard of care. 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.

Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.5.9.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for anti-cancer treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

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

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

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.

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

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.9.4). For anti-cancer treatment, 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.

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

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

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

Patient-Reported Outcome Data

Adverse event reports will not be derived from symptom reporting within the DPM solution, PRO-CTCAE or other PRO data by the Sponsor. Sites are not expected to review the DPM solution, PRO CTCAE or other PRO data for adverse events.

5.5.9.4 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 device or procedure:

- Serious adverse events (defined in Section 5.5.9.2; see Section 5.5.9.4 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.5.9.2; see Section 5.5.9.4 for details on reporting requirements)
- Pregnancies (see Section 5.5.9.4 for details on reporting requirements)

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

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

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

Medical Monitors and Emergency Medical Contacts

To ensure the safety of study *patients, access to* Medical *Monitors is* available 24 hours per day, 7 days per week. *Details will be provided separately. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week.* The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

Events that Occur prior to Starting Anti-cancer Treatment

After informed consent has been obtained but prior to initiation of anti-cancer treatment, only serious adverse events caused by a protocol-mandated intervention should be

reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

Events that Occur after Starting Anti-cancer Treatment

After initiation of anti-cancer treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of Atezolizumab and for 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow-up beyond this time point (see Section 5.5.9.3). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.5.9.6.

Reporting Requirements for Pregnancies

Pregnancies in Female Participants

Female participants 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 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow-up beyond this time point. 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 anti-cancer treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in

the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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

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).

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

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

Congenital Anomalies/Birth Defects

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

5.5.9.5 Follow-up of *Patients* after Adverse Events

Investigator Follow-up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or 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 anti-cancer treatment or study-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.5.9.3), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.5.9.4.

Sponsor Follow-up

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

5.5.9.6 Adverse Events That Occur after the Adverse Event Reporting Period

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of Atezolizumab or 30 days after the last dose of an alternative cancer therapy that has started prior to the 24-week time point and has continued follow up beyond this time point), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to anti-cancer 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.

5.5.9.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, And Ethics Committees

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure

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

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

5.6 INTERVENTION, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

5.6.1 Study Intervention Discontinuation

5.6.1.1 DPM Discontinuation (Cohort A and Cohort B)

Patients must permanently discontinue use of the DPM solution if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the *patient's* safety if he or she continues to receive study intervention
- Investigator or Sponsor determination that intervention discontinuation is in the best interest of the *patient*
- Permanent device malfunction, if *patient* has access to one usable device only
- *Patient treated with a protocol approved study intervention (see Section 5.3.1.1.2 and Section 5.3.1.2.6)*

The primary reason for DPM discontinuation should be documented on the appropriate eCRF. *Patients* who discontinue use of the DPM will not be replaced.

5.6.1.2 Atezolizumab SC Discontinuation (Cohort B)

Patients in Cohort B must permanently discontinue Atezolizumab SC if they experience any of the following:

- Intolerable toxicity related to Atezolizumab SC, 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 the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive Atezolizumab SC
- Investigator or Sponsor determination that Atezolizumab SC discontinuation is in the best interest of the *patient*
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final scheduled treatment. An earlier visit may be used as the treatment discontinuation visit if a local assessment of tumor response indicates a loss of clinical benefit.

Refer to the schedule of activities for details on follow-up assessments to be performed for *patients* who permanently discontinue Atezolizumab SC. If a *patient* requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

5.6.2 *Patient* Discontinuation from the Study

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

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

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

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.

5.6.3 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 participants
- *Patient* enrollment is unsatisfactory

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

5.6.4 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 guidelines for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

6. ASSESSMENT OF SAFETY

Text in Section 6.1 refers to the assessment of safety of the DPM solution for Cohorts A and B. Text on the assessment of anti-cancer treatment associated adverse events as part of the efficacy analyses for Cohort A is provided in Section 5.5.9 and text on the assessment of the safety of Atezolizumab for Cohort B is provided in Section 6.2.

6.1 DEVICE SAFETY (COHORTS A AND B)

6.1.1 Safety Plan

The anticipated important safety risks for the DPM solution are outlined below.

Several measures will be taken to ensure the safety of *patients* in this study. *Patients* will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse device *incidents*. In addition, guidelines for managing adverse device *incidents*, including criteria for DPM solution discontinuation, are provided below.

6.1.1.1 Risks Associated with the Kaiku Health DPM Solution

Kaiku Health is compliant with industry regulations and is a CE-marked Class IIa medical device in the European Union, *in Australia Kaiku Health is registered in the ARTG via its parent company Elekta (ARTG No 337499),* and is fully GDPR compliant.

Potential risks have been assessed according to the manufacturer‘s risk assessment processes and categorized by severity and probability of occurrence. Risks that remain after mitigation strategies were put in place are considered residual risks. The residual risks for this study are listed below.

- **Non-transmission of information:** The intended recipient of information does not or cannot view the information in a timely manner. This may be caused e.g., by the user not accessing Kaiku Health in a timely manner despite notifications, availability issues with Kaiku Health, technical issues with Kaiku Health in displaying the information.
- **Incorrect self-management instructions:** Self-management instructions presented to a user of Kaiku Health may not be applicable to the particular situation, e.g., due to misconfiguration of Kaiku Health, participant misinterpretation of the given instructions, or erroneous algorithm implementation.
- **Misuse of free text field for reporting of listed symptoms:** If symptoms listed in the questionnaire are reported via the free text field, the participant will not receive self-management instructions that are provided with the listed symptom.
- **Information security:** Various risks that impact the confidentiality, integrity, and/or availability of the sensitive personal data processed by Kaiku Health.

Due to the residual risks above, the following warnings are presented to the users of Kaiku Health within the application:

1. Kaiku Health is not monitored in real-time by the clinical staff, it is intended only for non-urgent communication. In urgent situations, contact your care unit or emergency number by phone.
2. In some special cases the guidance and self-care instructions that Kaiku Health provides might not apply to you. If you have any questions regarding your care, or your symptoms and their management, we kindly ask you to contact your care team.
3. If you do not receive a response from your care unit within a reasonable time, please contact the care unit via phone.
4. Risks related to confidentiality, integrity, and/or availability of the personal data processed by Kaiku Health cannot be completely eliminated. If you suspect that your personal data has been compromised, please contact Kaiku Health support.

If the DPM solution fails, participants will receive local SOC. At all times, the *patient* may contact their care provider using the means available under the local SOC.

6.1.1.2 Management of *Patients* Who Experience Adverse Device *Incidents*

DPM Solution Interruption or Discontinuation

The DPM solution may be temporarily interrupted or permanently discontinued in *patients* who experience adverse device *incidents* considered to be related to the device or associated procedure.

Management Guidelines

If a *patient* experiences an adverse device *incident* related to one of the residual risks mentioned above, medical care should be provided according to the clinician's best judgement.

For *patients* who experience anxiety which exceeds previously reported levels or occurs for the first time and is persistent, medical care should be provided as per clinical judgement and treatment may be temporarily interrupted.

6.1.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording adverse device *incidents* including *field safety corrective actions (FSCA).*

In this clinical trial, the Kaiku DPM Solution and the Roche modules are used in their intended purpose. Thus, clinical trial medical device safety reporting does not apply.

To report any medical device adverse incident, the device manufacturers processes are used.

6.1.2.1 *Medical Device* Adverse *Incident*

An adverse *incident* is *an* event that *caused,* or *almost caused, an injury to a patient or other person*, or *a wrong* or *delayed diagnosis and treatment of a patient.* Adverse device *event reporting in regard to Kaiku Health will be as per the CE mark and local regulations for the reporting of such events.* Per the *DPM* device's labelling, no adverse device *incidents* are anticipated.

6.1.3 Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all *incidents* (see Section 6.1.2 for definitions) are reported to the *manufacturer* in accordance with instructions provided in this Section 6.1.3.

For each *incident reported to* the *manufacturer* the investigator will make an assessment of seriousness (see Section 6.1.3.2 for adverse device effects) and causality (only applicable for adverse device effects, see Section 6.1.3.3).

6.1.3.1 Device *Incident* Reporting Period

Investigators will seek information on adverse device *incidents* and device deficiencies at each patient contact. All events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and *reported to the device manufacturer*.

After initiation of study treatment, all adverse device effects will be reported until 30 days after study end.

6.1.3.2 Assessment of Severity of Adverse Device *Incidents*

Guidelines for classifying the severity of adverse device *incidents* are provided in Table 5. This information is used to determine acceptability thresholds for anticipated adverse device *incidents*.

Table 5 Severity Classification for Adverse Device *Incidents*

Grade		Severity
1	Negligible	No impact or at most inconvenience or temporary discomfort
2	Moderate	Results in temporary injury or impairment, not requiring professional medical intervention[a]
3	Severe	Results in temporary injury or impairment requiring professional medical intervention
4	Critical	Results in permanent impairment or life-threatening injury
5	Catastrophic	Results in *patient* death

[a] Clinical or diagnostic observations only are not considered an intervention

6.1.3.3 Assessment of Causality of Adverse Device *Incidents*

Investigators should use their knowledge of the *patient*, the circumstances surrounding the event, and an evaluation of any potential alternative cause to determine whether an adverse device *incident* is considered to be related to the device or device-related procedure. The guidelines provided in Table 6 should be used to assess the causality of adverse device effects.

Table 6 Assessment of Event Relationship to Device or Device-Related Procedure

Relationship	Criteria for Classification
Not related [a]	• Event has no temporal relationship with the use of the device, or the procedures related to application of the device; • Event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • Discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; • Event involves a body site or an organ not expected to be affected by the device or procedure; • Event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • Event does not depend on a false result given by the device used for diagnosis, when applicable.
Possible	• Relationship with the use of the device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	• Relationship with the use of the device or comparator, or the relationship with procedures seems relevant and/or the event cannot reasonably be explained by another cause.

Table 6 Assessment of Event Relationship to Device or Device-Related Procedure (Cont)

Causal relationship	Event is associated with the device or comparator or with procedures beyond reasonable doubt when:
	• Event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• Event has a temporal relationship with device use/application or procedures;
	• Event involves a body site or organ that:
	  ○ The device or procedures are applied to;
	  ○ The device or procedures have an effect on;
	• Event follows a known response pattern to the medical device (if the response pattern is previously known);
	• Discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
	• Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
	• Harm to the participant is due to error in use;
	• Event depends on a false result given by the device used for diagnosis, when applicable.

[a] Complications of procedures are considered to be not related if said procedures would have also been applied to participants in the absence of medical device use/application.

6.1.3.4 Procedures for *Reporting* Adverse Device *Incidents*

Investigators should use correct medical terminology/concepts when *reporting* adverse device *incidents to* the *manufacturer.* Avoid colloquialisms and abbreviations. Only one adverse device effect term should be *reported per report. Multiple effects in one email/report should be avoided. As a minimum site number, patient number, reporter name, incident description and current outcome are to be reported. Kaiku Health adverse device incidents should be reported to Kaiku Health Oy: support+ade@kaikuhealth.com*

Patient-Reported Outcome Data

Adverse device effect reports will not be derived from symptom reporting within the DPM Solution, PRO-CTCAE or other PRO data by the Sponsor.

6.2 ATEZOLIZUMAB SAFETY (COHORT B)

6.2.1 Safety Plan

The safety plan for *patients* in this study is based on clinical experience with Atezolizumab and rHuPH20 in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 6.2.1.1 and Section 6.2.1.2).

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 SC 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. Atezolizumab SC administration in the *at-home treatment* setting will be performed by a qualified mobile HCP with access to adequate equipment to manage adverse events (AEs). A phone or video call will be established between the qualified mobile HCP and the treating clinic HCPs during Atezolizumab SC administration in the *at-home treatment* setting. Additional risk mitigation strategies for administration in the *at-home treatment* setting are outlined in Section 1.7. Guidelines for managing *patients* who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 7. Refer to Sections 6.2.2–6.2.7 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

6.2.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 7 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for Atezolizumab.

Guidelines for managing *patients* who experience anticipated adverse events are provided in Appendix 7.

6.2.1.2 Risks Associated with rHuPH20

rHuPH20 is co-formulated with Atezolizumab. rHuPH20 should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Refer to the rHuPH20 U.S. Package Insert for more details regarding the full safety profile of rHuPH20, including boxed warnings and contraindications (HYLENEX® recombinant (hyaluronidase human injection) U.S. Package Insert, Halozyme, Inc.).

Refer to Appendix 7 for adverse *event* management guidelines for Atezolizumab.

6.2.2 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 6.2.4.

6.2.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 6.2.3.5.9 and 6.2.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

6.2.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 6.2.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the *patient's* ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the *patient* or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 6.2.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 6.2.3.5.7)
- Suspected transmission of an infectious agent by a 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 the study treatment is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

6.2.2.4 Selected Adverse Events

Injection-Site Reactions

With SC administration, local reactions at site of injection (erythema, pruritus, edema, rash, and pain) may occur. In case of severe injection-site reactions, unscheduled photographs will be taken. Photographs should include a label showing the *patient's* identification number, date and time of calendar date, and a centimeter ruler to provide scale. Efforts will be made to standardize the photography with regard to parameters such as angle, light, distance from body, and settings.

See Section 6.2.3.5.1 for instructions on reporting injection-related reactions and infusion related reactions.

6.2.3 Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all adverse events (see Section 6.2.2.1 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 6.2.4–6.2.6. The investigator is also responsible for reporting medical device complaints (see Section 6.1).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 6.2.2.2 for seriousness criteria), severity (see Section 6.2.3.3), and causality (see Section 6.2.3.4).

6.2.3.1 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 6.2.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 6.2.6.

6.2.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant 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?"

6.2.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity.

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

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

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

Note: Based on the most recent version of NCI CTCAE (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 6.2.4.2 for reporting instructions), per the definition of serious adverse event in Section 6.2.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6.2.4.2 for reporting instructions), per the definition of serious adverse event in Section 6.2.2.2.

6.2.3.4 Assessment of Causality of Adverse Events

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

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

Table 8 Causal Attribution Guidance

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

6.2.3.5 Procedures for Recording Adverse Events

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

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

6.2.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

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

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

If a *patient* experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event 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 7.

6.2.3.5.2 Diagnosis Versus Signs and Symptoms

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

6.2.3.5.3 Adverse Events That are Secondary to Other Events

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

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

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

6.2.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between *patient* evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see

Section 6.2.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

6.2.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 6.2.3.5.4 for details on recording persistent adverse events).

6.2.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 6.2.3.5.4 for details on recording persistent adverse events).

6.2.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ 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 6.2.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 6.2.4.2).

6.2.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 6.2.3.1) that are attributed by the investigator solely to progression of NSCLC 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 6.2.4.2).

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 6.2.6.

6.2.3.5.9 Pre-existing Medical Conditions

A pre-existing 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 pre-existing 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

6.2.3.5.10 Lack of Efficacy or Worsening of NSCLC

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of NSCLC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non-small cell lung cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on investigator assessment according to local SOC. 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.

6.2.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 6.2.2.2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a pre-existing 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 participant has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

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

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

6.2.3.5.12 Cases Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

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

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

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2). 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

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

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

Patient-Reported Outcome Data

Adverse event reports will not be derived from symptom reporting within the DPM solution, PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the DPM solution, PRO-CTCAE or other PRO data for adverse events.

6.2.4 Immediate Reporting Requirements from Investigator to Sponsor

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

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 6.2.2.2; see Section 6.2.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 6.2.2.3; see Section 6.2.4.2 for details on reporting requirements)
- Pregnancies (see Section 6.2.4.3 for details on reporting requirements)

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

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

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

6.2.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study *patients*, an *access to* Medical *Monitor is* available 24 hours per day, 7 days per week. *Details will be provided separately. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week.* The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

6.2.4.2.1 Events That Occur prior to Study Treatment Initiation

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

6.2.4.2.2 Events That Occur after Study Treatment Initiation

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

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

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

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 6.2.6.

6.2.4.3 Reporting Requirements for Pregnancies

6.2.4.3.1 Pregnancies in Female Participants

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

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

6.2.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

6.2.4.3.3 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 participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.2.4.2).

6.2.5 Follow-Up of *Patients* after Adverse Events

6.2.5.1 Investigator Follow-Up

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

During the adverse event reporting period (defined in Section 6.2.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 6.2.4.3.

6.2.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

6.2.6 Adverse Events That Occur after the Adverse Event Reporting Period

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

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

6.2.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

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

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

Drug	Document
Atezolizumab	Atezolizumab Investigator's Brochure

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

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

7. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

7.1 COHORT A

The Full Analysis Set will consist of all randomized participants, in line with the *intent-to-treat (*ITT*)* principle. Randomized *patients* who receive incorrect assignment of DPM

from that intended will be summarized in the group according to their planned randomization.

The primary analysis population for safety is the Safety Analysis Population defined as all participants who received at least one dose of the anti-cancer regimen containing Atezolizumab (IV) and/or used the DPM solution. All *patients* who were given access to the DPM solution will be included in the DPM arm.

[redacted]

OS will be analysed at the time of the primary analysis. If less than 50% of *patients* have been followed up for 12 months at the time of the primary analysis, an OS follow-up analysis may take place. The study is not powered to demonstrate a statistically significant difference in OS and this is for the purpose of assessing the exploratory efficacy objective of OS.

Hypothesis tests will be [redacted] with a significance level of [redacted]%.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of the anti-cancer regimen containing Atezolizumab (IV) and the Roche DPM Atezolizumab Module.

Further details of all analyses will be provided in the Statistical Analysis Plan (SAP).

7.2 COHORT B

The Full Analysis Set will consist of all enrolled *patients*.

The Evaluable Population is defined as *patients* who completed three cycles of Atezolizumab SC in the hospital setting.

The primary analysis population for safety is the Safety Analysis Population defined as all *patients* who received at least one dose of Atezolizumab SC and/or used the DPM solution.

[redacted]

7.3 DETERMINATION OF SAMPLE SIZE

7.3.1 Cohort A

The focus of this cohort is hypothesis testing, and the primary endpoint of change of Week 12 value from baseline in the *patient*-reported Symptom Interference Score from the MDASI Core Items was used to determine the sample size of the study. A mean difference of 8 points is assumed to be clinically meaningful (Cocks et al. 2011).

A sample size of 400 randomized participants [redacted] provides [redacted]% power to detect a difference in means between study arms in the change from baseline at Week 12 in the MDASI Total Interference Score of at least 8 points, assuming a [redacted] and a standard deviation (SD) of approximately 25 points.

The assumption for mean change and SD is based on both the responsiveness of the MDASI Total Interference Score reported by Shi et al. 2016 and analyses of historical data from pivotal trials from GHS scale from EORTC QLQ-C30.

Shi et al. reported a moderate effect size of 0.65 in patients that received Chemoradiation with mean change from baseline of 12 and SD of 24 points (Shi et al. 2016). In total 110 patients completed MDASI at baseline and after the Chemoradiotherapy. Considering the small sample size reported in the study and the fact those reflect intra-participant comparison we also took into account historical data from GHS scale from EORTC QLQ-C30 as the EORTC IL6 GHS/QoL scale will be included as a PRO in this study.

The assumption for the SD is based on analyses of historical data from pivotal trials of Atezolizumab in the same indications to be studied (IMpower110 [mNSCLC], IMpower133 [ES-SCLC], and IMbrave150 [HCC]). Based on this data, the SD of the change from baseline to Week 12 scores range from 17.6 to 24.2. For the purpose of this sample size calculation, 25 points is used as a conservative estimate. This also corresponds to published sample size assumptions relating to the EORTC QLQ-C30 questionnaire scores which typically power to target an effect size of 0.4 for these PRO endpoints, corresponding to a mean difference of 10 points divided by a SD of 25 (10/25=0.4) (Basch et al. 2016; Basch et al. 2014).

Table 9 summarizes the reference data from the pivotal trials for the EORTC QLQ-C30 GHS scale score for *patients* treated with an Atezolizumab regimen (and the respective combination partners as applicable) with available data at cycles corresponding to the Week 12 time point.

Table 9 Analysis of EORTC QLQ-C30 Global Health Status Score from Historical Atezolizumab Pivotal Trails

Trial Name	Indication	Baseline Score (SD)	Mean Week 12[a] Score (SD)	Mean Change from Baseline to Week 12[a] Score (SD)
IMpower110	mNSCLC	n=267 63.7 (20.0)	n=54 67.9 (23.3)	n=51 2.0 (21.2)
IMpower133	ES-SCLC	n=238 54.1 (23.3)	n=188 64.9 (18.5)	n=180 10.6 (24.2)
IMbrave150	HCC	n=316 70.6 (21.1)	n=260 69.8 (19.8)	n=253 -3.3 (17.6)

ES-SCLC =extensive-stage small-cell lung carcinoma; mNSCLC =metastatic non-small cell lung cancer; HCC =hepatocellular carcinoma; SD =standard deviation.

[a]IMpower110, IMpower133 and IMbrave150: Week 12 corresponds to pre-Cycle 5 PRO assessment.

In order to ensure that the study population includes a representation of *patients* across all three disease indications, enrollment will be capped for any one indication exceeding [redacted] i.e., once [redacted] *patients* of any one indication are enrolled, enrollment into strata corresponding to that disease indication will close and the study will continue to enroll participants from the remaining indications.

7.3.2 Cohort B

For this cohort, [redacted] participants will be enrolled. Since this cohort is intended to be an exploratory pilot study, no formal sample size calculation was performed. Therefore, no formal hypothesis testing will be performed on the primary endpoint of *at-home treatment* adoption at Cycle 6.

7.4 SUMMARIES OF CONDUCT OF STUDY (ALL COHORTS)

Enrollment and reasons for discontinuation from the study will be summarized by study arm for the ITT population. Major protocol deviations, including major deviations of inclusion and/or exclusion criteria, will be summarized by study arm and evaluated for their potential effects on the interpretation of study results.

Anti-cancer treatment administration and DPM administration, and reasons for discontinuation from study intervention or DPM usage will be summarized.

7.5 SUMMARIES OF STUDY GROUP COMPARABILITY (ALL COHORTS)

Summaries of study group comparability will be based on the ITT population.

Demographic characteristics (such as age, sex, race/ethnicity), baseline disease characteristics (such as ECOG performance status, PD-L1 status) will be summarized by study arm for the ITT population, including the randomization stratification factors. Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median and range. Descriptive summaries of categorical data will present frequencies and percentages.

Subsequent anti-cancer therapy will also be summarized. Previous and concurrent diseases and medications will also be summarized.

7.6 EFFICACY ANALYSES

7.6.1 Cohort A

The primary population for all primary and secondary efficacy endpoints will be the ITT population (Full Analysis Set). Subgroup analyses will be performed for important baseline covariates to be specified in the SAP. These will include separate analyses of each disease indication subgroup.

7.6.1.1 Primary Efficacy Endpoint

The primary estimand corresponding to the primary cohort objective is defined as follows:

Population

Participants who have not received prior systemic therapy with the following indications will be included: mNSCLC, ES-SCLC, and HCC. The study population will comprise a maximum of [redacted]% from each of these cancer indications.

Primary endpoint (variable)

Total Interference Score from MDASI. The score corresponds to the mean of six interference items (Questions 14 to 19 referring to interference in general activity, mood, work, relations with other people, walking and enjoyment of life), the mean is then linearly transformed so the score ranges from 0 to 100.

Treatments

Cohort A:

Experimental: Local SOC support with use of a DPM solution plus treatment with a locally approved anti-cancer regimen containing Atezolizumab (IV) as in Table 1 for each indication.

Control: Local SOC support without use of a DPM solution plus treatment with a locally approved anti-cancer regimen containing Atezolizumab (IV) as in Table 1 for each indication.

Intercurrent events

- Atezolizumab (IV) regimen discontinuation prior to Week 12
- New anti-cancer therapy prior to Week 12
- Termination of use of DPM solution prior to Week 12
- Non-treatment/DPM related study discontinuations prior to Week 12
- Death prior to Week 12

Handling of intercurrent events

- Atezolizumab (IV) regimen discontinuation prior to Week 12: treatment-policy
- New anti-cancer therapy prior to Week 12: treatment policy
- Termination of use of DPM solution prior to Week 12: treatment policy
- Non-treatment/DPM related study discontinuations prior to Week 12: hypothetical
- Death prior to Week 12: while alive (last score before death)

Summary measure: Mean difference in change of Week 12 value from baseline

The Full Analysis Set will consist of all randomized participants (in line with the ITT principle). Randomized participants who receive incorrect assignment of DPM from that intended will be summarized in the arm according to their planned randomization.

The primary comparison of interest is the mean difference in change of the Week 12 value from baseline of the Total Symptom Interference score from the MDASI core items. The primary efficacy analysis for this cohort will compare the Roche DPM Atezolizumab Module plus local SOC support and a locally approved anti-cancer regimen containing Atezolizumab (IV) with local SOC support and a locally approved anti-cancer regimen containing Atezolizumab (IV) only at Week 12. The following null and alternative hypotheses will be tested at a [redacted]:

- H_0: $\mu_{DPM} = \mu_{SOC}$ versus
- H_a: $\mu_{DPM} \neq \mu_{SOC}$

for which the μ_{DPM} and μ_{SOC} refer to the mean change from baseline for Roche DPM Atezolizumab Module and local SOC support and local SOC support only, respectively.

The primary study objective is to demonstrate superiority of the experimental over the control treatment.

Primary analysis

A mixed model repeated measures (MMRM) analysis adjusting for baseline Total Symptom Interference score, disease indication and ECOG performance status will be used to estimate the mean change from baseline to Week 12 for the primary endpoint.

The model will include the change from baseline in Total Symptom Interference score as the dependent variable. The effects in the model will include baseline Total Symptom Interference score, disease indication, ECOG performance status, treatment arm, visit, and treatment-by-visit interaction. Visit week will be treated as the repeated variable within a participant.

The difference in the change from baseline of the participants randomized to the DPM arm from participants randomized to the comparator arm will be estimated at each time point. The 95% CI and p-value for treatment difference will be determined.

All efforts will be made to minimize missing data. For those participants with an intercurrent event handled by treatment policy, efficacy data including PRO assessments will still be collected for the primary and secondary endpoints until Week 24. For participants who die prior to the Week 12 assessment, the last score before death will be used. This may include the baseline value.

Data affected by intercurrent events following a hypothetical strategy (i.e., non-treatment/DPM related study discontinuations prior to Week 12), as well as purely missing Week 12 PRO assessments which are considered to be missing at random, the following imputation strategy will be used:

1. Imputation step: Hypothetical values will be imputed *m* times based on statistical modeling that will consider the Total Symptom Interference baseline score, disease indication and ECOG performance status as predictor variables.
2. Analysis step: Each of the resulting *m* data sets will be analyzed using the statistical model above, which will provide an estimate of treatment difference.
3. Pooling step: The results from the *m* data sets will be combined leading to an overall estimate of the treatment effect and associated 95% confidence intervals and *p*-values.

More details, including m and further details of the multiple imputation strategy, will be specified in the statistical analysis plan.

7.6.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will not be formally tested; therefore, no multiplicity adjustment is performed. P-values may be presented for descriptive purposes only.

7.6.1.2.1 Hospitalizations

The number and percentage of participants who are hospitalized due to an AE will be summarized overall and over time by treatment arm for the ITT population. Reason for hospitalization will be based on information documented in the eCRF. The number of cumulative days hospitalized due to SAEs will also be summarized overall and by treatment arm for the ITT population. Summaries may be presented by country or by pre-defined groupings of countries. More details will be provided in the SAP.

In order to account for competing events of death before observation of a hospitalization, as well as the varying follow-up for hospitalizations of participants, hospitalization probability estimates will be based on the cumulative incidence function. This will be estimated using the non-parametric Aalen-Johansen estimator.

A plot of the cumulative incidence function (CIF) will be produced to display the probability of a hospitalization over time. In order to compare treatment groups, the relative risk at Week 6, Week 12, Week 18 and Week 24 will be calculated based on these estimated probabilities.

To assess the effect of DPM solution on estimated probabilities over the entire time-span, subdistribution hazards corresponding to the cumulative incidence functions will be compared using a Gray's test. To assess the effect of the DPM solution on the hazard of hospitalization, the event-specific hazard ratio for hospitalization will be presented.

Descriptive summaries will also be provided for hospitalizations for any reason.

7.6.1.2.2 Unscheduled visits to the ER or clinic visits for symptom management

The number and percentage of participants who have unscheduled visits to the ER or unscheduled clinic visits for non-administrative reasons (e.g., symptom management) will be summarized overall and over time by treatment arm for the ITT population. This will be based on information documented in the eCRF. Summaries may be presented by country or by pre-defined groupings of countries. More details will be provided in the SAP.

In order to account for competing events of death before unscheduled ER or clinic visits, as well as the varying follow-up of participants, this endpoint will be analyzed using the same methodology as specified for hospitalizations (see Section 7.6.1.2.1).

7.6.1.2.3 Incidence, nature, and severity of anti-cancer treatment associated AEs

Anti-cancer treatment associated AEs will be coded using MedDRA and summarized by mapped term and appropriate thesaurus level. All AEs and routine laboratory parameters will be assessed according to the NCI-CTCAE v 5.0 grading system.

The following safety parameters will be summarized in tables to evaluate and compare the safety profile of participants treated with a locally approved anti-cancer regimen containing Atezolizumab (IV) in combination with the Roche DPM Atezolizumab Module plus local SOC support versus a locally approved anti-cancer regimen containing Atezolizumab (IV) with local SOC support only in terms of:

- AEs including AEs leading to dose modifications or interruptions, or withdrawal of anti-cancer treatment, and death

- AEs related to anti-cancer treatment and adverse events related to study device
- Severe, serious, and selected immune-related adverse events (pneumonitis, thyroid disorders, diarrhea or colitis, nephritis, rash, and hepatitis)
- Deaths
- Laboratory parameters and abnormalities
- Vital signs

AEs will generally be reported according to the most extreme severity; however summaries will also be produced to present changes in the severity of selected adverse events. More details will be provided in the SAP.

7.6.1.2.4 Grade ≥ 3 AEs

The number and percentage of participants who have Grade ≥ 3 AEs will be summarized overall and over time by treatment arm.

In order to compare rates between study arms and to account for competing events of death before observation of a Grade ≥ 3 AE, as well as the varying follow-up for AEs of participants, this endpoint will be analyzed using the same methodology as specified for hospitalizations (see Section 7.6.1.2.1).

7.6.1.2.5 SAEs

The number and percentage of participants who have SAEs will be summarized overall and over time by study arm.

In order to compare rates between study arms and to account for competing events of death before observation of a SAE, as well as the varying follow-up for AEs of participants, this endpoint will be analyzed using the same methodology as specified for hospitalizations (see Section 7.6.1.2.1).

7.6.1.2.6 Weighted Toxicity Score

The weighted toxicity score (WTS) was first defined by Carbini et al. in 'A Method to Summarize Toxicity in Cancer Randomized Clinical Trials' (Carbini et al. 2018).

The WTS is defined as the sum of the proportion of participants with toxicities (Grade 1 to 4) weighted by a severity index, which increases from Grade 1 to Grade 4 for a specific toxicity. The weight for each toxicity grade is multiplied by the proportion of participants with that toxicity grade, and all products are added to yield a toxicity score for a particular adverse event. The WTS for a treatment arm is the sum of all individual toxicity scores for that arm. Adverse event weighting will be pre-specified in the SAP, with pre-specified adverse events of interest potentially being more heavily weighted.

The WTS will be summarized by study arm using descriptive statistics, i.e., mean, standard deviation, median, minimum and maximum. The WTS will be compared across study arms using a t-test for descriptive purposes.

7.6.1.2.7 Interruption, Modification, or Discontinuation due to AEs

The number and percentage of participants who have anti-cancer treatment dose interruptions, modifications or discontinuations due to AEs will be summarized overall and over time by study arm.

In order to compare rates of anti-cancer treatment discontinuation due to AEs between study arms and to account for competing events of death or discontinuation of anti-cancer treatment due to any other reason, as well as the varying follow-up for AEs of participants, this endpoint will be analyzed using the same methodology as specified for hospitalizations (see Section 7.6.1.2.1).

7.6.1.2.8 Selected Immune-Related Adverse Events

The number and percentage of participants who have selected immune-related AEs will be summarized overall and over time by study arm. Selected immune-related AEs are listed in Section 3.1.1.2.

7.6.1.2.9 EORTC IL6 GHS/QoL

Change from baseline in EORTC IL6 GHS/QoL score will be analyzed.

EORTC IL6 GHS/QoL scores and change from baseline will be summarized descriptively using means, standard deviations, medians, and range, by treatment arm at baseline and across time.

7.6.1.2.10 *Patient*-reported health status utility (EQ-5D-5L)

Change from baseline in EQ-5D-5L VAS score will be analyzed.

EQ-5D-5L VAS scores and change from baseline will be summarized descriptively using means, standard deviations, medians, and range, by treatment arm at baseline and across time

7.6.1.2.11 MDASI Symptom Severity Score

Change from baseline in MDASI Symptom Severity Score will be analyzed.

MDASI Symptom Severity scores and change from baseline will be summarized descriptively using means, standard deviations, medians, and range, by treatment arm at baseline and across time.

7.6.1.3 Exploratory Efficacy Endpoints

7.6.1.3.1 *Patient*-reported satisfaction of healthcare treatment

Change from baseline in the scores of care convenience and transition will be analyzed *using EORTC specific complementary outpatient module (EORTC OUT-PATSAT7).*

Care convenience and transition scores and change from baseline will be summarized descriptively using means, standard deviations, medians, and range, by treatment arm at baseline and across time.

7.6.1.3.2 Time to discontinuation of treatment

TTD is defined as the time from the date of randomization to the date of discontinuation of Atezolizumab (IV) regimen for any reason. Patients who are still ongoing treatment with an Atezolizumab (IV) regimen at the time of analysis will be censored at the date of last administration of the last administered component of the Atezolizumab (IV) regimen. The comparison of TTD will be made regardless of whether a patient progresses or receives a new anti-cancer therapy prior to discontinuation of the Atezolizumab (IV) regimen.

The Kaplan-Meier method will be used to estimate the median TTD for each treatment arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the study arms. A stratified Cox proportional regression model will be used including study arm in order to provide an estimate of the treatment effect of DPM expressed as a HR, as well as a 95% CI.

[redacted]

In this analysis, intercurrent events and their handling are defined as follows:

- Disease progression prior to treatment discontinuation: treatment policy
- New anti-cancer therapy prior to treatment discontinuation: treatment policy
- Death while on treatment: composite strategy (death on treatment will be classed as a treatment discontinuation).

In addition, a time to event analysis of time to discontinuation of the first component of the treatment regimen for any reason, including premature discontinuation of induction chemotherapy, if applicable, will be performed using the same methodology.

7.6.1.3.3 Time to clinical progression or death (PFS)

PFS is defined as the time from the date of randomization to the date of clinical progression or death due to any cause. Investigators will be asked whether the participant has clinically progressed since the last visit and this will be documented by the investigator on the eCRF. $Patients$ who are not reported as having progressed or died at the time of analysis will be censored at the date when they were last assessed to be clinically stable / progression free. Participants who do not have post-baseline information will be censored at the date of randomization. PFS will be analyzed using the same methodology as specified for TTD (see Section 7.6.1.3.2).

In this analysis, intercurrent events and their handling are defined as follows:

- Discontinuation of treatment prior to clinical or symptomatic progression: treatment policy
- New anti-cancer therapy prior to clinical or symptomatic progression: treatment policy

7.6.1.3.4 Overall Survival

OS is defined as the time from the date of randomization to the date of death due to any cause. Participants who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Participants who do not have post-baseline information will be censored at the date of randomization. OS will be analyzed using the same methodology as specified for TTD (see Section 7.6.1.3.2). A survival follow-up analysis may be performed based on more mature data.

In this analysis, intercurrent events and their handling are defined as follows:

- Discontinuation of treatment prior to death: treatment policy
- Disease progression prior to death: treatment policy
- New anti-cancer therapy prior to death: treatment policy

7.6.1.3.5 Utilization of concomitant medication of special interest for management of AEs (e.g., steroids for immune-related adverse events (irAEs); diarrhea medication)

Concomitant medications will be summarized by study group. Baskets of medications of interest will be pre-defined and summaries will be produced to present the number and percentage of participants administered these medications due to specific AEs such as irAEs and diarrhea. More details will be provided in the SAP.

7.6.1.3.6 Anti-cancer treatment dose intensity and exposure

Anti-cancer treatment administration will be summarized by duration of treatment and cumulative dose. In addition, treatment exposure will be summarized including the number of doses received, dose intensity, and the percentage of planned dose.

7.6.1.3.7 Utilization

Summaries will be produced to describe the utilization of Roche DPM Atezolizumab Module*, and DPM platform,* and/or local SOC support.

Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median and range. Descriptive summaries of categorical data will present frequencies and percentages. Summaries will be produced overall and over time.

The following variables will be summarized for the DPM arm only:

- DPM Utilization:
  - Percentage of enrolled *patients* using DPM weekly
  - Duration of use for each participant or on average by all participants (in weeks)

The following endpoints will be summarized over time by weeks referenced to treatment start/DPM assignment, i.e., Week 1, Week 2, etc.:

- Time spent by *patients* vs. care teams on the platform (in minutes)

- Number of logins
- Time spent by *patients* on completing the symptom questionnaire (in minutes)
- Time spent by *patients* on self-management or educational materials; ranking of most accessed materials
- Number of symptom questionnaires filled in by *patients*
- Number of *patients* for which a symptom alert was triggered. Time (in hours) until an alerted vs. non-alerted symptom questionnaire was reviewed by care teams
- Number of messages sent between care teams and *patients*

7.6.2 Cohort B

7.6.2.1 Primary Efficacy Endpoint

The primary estimand corresponding to the primary cohort objective is defined as follows:

Population

Participants with resected Stage IIB-IIIB (early-stage) NSCLC who have had a complete resection of NSCLC, are adequately recovered from surgery and who have completed up to four cycles of adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence will be included.

For efficacy analysis the Evaluable Population as defined in Section 7.2 will be used.

Primary endpoint (variable)

Binary assessment of *at-home treatment* adoption at Cycle 6 in patients who are continuing to receive Atezolizumab SC treatment (1 = adoption; 0 = non adoption).

Adoption is defined as a decision by the investigator and the participant to continue to receive Atezolizumab SC in the *at-home treatment* setting rather than Atezolizumab SC in the hospital setting.

If a *patient* or investigator decides to terminate the Atezolizumab SC in the *at-home treatment* setting while continuing Atezolizumab SC in the hospital setting before Cycle 6, they will be classified as not adopting (0).

Treatments

Cohort B:

Experimental: Three cycles of Atezolizumab SC in the hospital setting followed by 13 cycles of Atezolizumab SC in the at-home *treatment* setting

Intercurrent events and handling

The following intercurrent events will be summarized descriptively:

- Atezolizumab SC discontinuation at a time after the last dose of Atezolizumab SC administered in the hospital setting and prior to Cycle 6
- Death at a time after the last dose of Atezolizumab SC administered in the hospital setting and prior to Cycle 6

For the primary endpoint these participants will not be included in the denominator.

Summary measure: Percentage of *at-home treatment* adoption at Cycle 6.

The primary endpoint of interest is *at-home treatment* adoption at Cycle 6. No hypothesis testing for this endpoint will be performed.

7.6.2.2 Exploratory Endpoints

7.6.2.2.1 *At-home treatment* adherence

At-home treatment adherence at Cycles 9, 12, and 15 will be calculated.

Adherence is defined as receiving Atezolizumab SC in the *at-home treatment* setting at certain cycle given that patient received Atezolizumab SC in the *at-home treatment* setting at Cycle 6.

7.6.2.2.2 Unscheduled visits to the ER or clinic visits for symptom management

The number and percentage of patients who have unscheduled visits to the ER or unscheduled clinic visits for non-administrative reasons (e.g., symptom management) within one day of SC administration will be summarized overall and over time for the ITT population. This will be based on information documented in the eCRF.

7.6.2.2.3 Number of hospitalizations within 1 day of SC administration due to SAEs

The number and percentage of *patients* who are hospitalized due to an SAE will be summarized overall and over time for the safety population. Reason for hospitalization will be based on information documented in the eCRF. The number of cumulative days hospitalized due to SAEs will also be summarized overall.

7.6.2.2.4 Interruption, modification, or discontinuation of Atezolizumab due to AEs occurring within 1 day of SC administration

The number and percentage of *patients* who have Atezolizumab dose interruptions, modifications or discontinuations due to AEs occurring within 1 day of SC administration will be summarized.

7.6.2.2.5 Incidence, nature, and severity of Atezolizumab SC associated AEs graded per-CTCAE v5.0 with particular focus on Grade ≥ 3 AEs and SAEs

Atezolizumab SC associated AEs will be coded using MedDRA and summarized by mapped term and appropriate thesaurus level. All AEs and routine laboratory parameters will be assessed according to the NCI-CTCAE v 5.0 grading system.

Relevant laboratory, vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be summarized. A shift table of selected laboratory tests will be produced to summarize the baseline and maximum post-baseline severity grade.

7.6.2.2.6 Reasons for not continuing in *at-home treatment* setting (questionnaire for participants / HCPs)

Reasons for not continuing in *at-home treatment* setting will be asked at the time of drop-out.

7.6.2.2.7 Anti-cancer treatment dose intensity and exposure

Anti-cancer treatment administration will be summarized by duration of treatment and cumulative dose. In addition, treatment exposure will be summarized including the number of doses received, dose intensity, and the percentage of planned dose.

7.6.2.2.8 Patient-Reported Outcomes

Change from baseline in EORTC IL6 GHS/QoL, EQ-5D-5L VAS, and MDASI Symptom Severity scores will be analyzed.

Scores and change from baseline will be summarized descriptively using means, standard deviations, medians, and range at baseline and across time.

7.7 SAFETY ANALYSES

7.7.1 Cohort A

The primary analysis population for safety is the Safety Analysis Population as described in Section Section 7. All adverse device effects occurring on or after the date of administration of the DPM solution, will be included in analyses.

Safety will be assessed through summaries of exposure to study device and adverse device effects.

Study device exposure (such as device use duration) will be summarized with descriptive statistics.

All adverse device effects, serious adverse device effects, and device deficiencies that could have led to a serious adverse device effect will be summarized.

7.7.2 Cohort B

The primary analysis population for safety is the Safety Analysis Population as described in Section 7. All adverse device effects occurring on or after the date of administration of the DPM solution, will be included in analyses.

Safety will be assessed through summaries of exposure to study device and adverse device effects.

Study device exposure (such as device use duration) will be summarized with descriptive statistics.

All adverse device effects, serious adverse device effects, and device deficiencies that could have led to a serious adverse device effect will be summarized.

8. DATA COLLECTION AND MANAGEMENT

8.1 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.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the 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.

8.2 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 participant 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.

8.3 ELECTRONIC *PATIENT*-REPORTED OUTCOME DATA

An app downloaded onto an electronic device will be used to capture PRO data. The app is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive participant data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

8.4 DEVICE DATA

For a full description of the *medical* device used in this study, refer to Section 2.3. Data will be collected within a cloud-based platform(s), for processing, analysis and storage, managed by the Device Manufacturer. Only identified and trained users access this system.

Device data may be analyzed on an ongoing basis for the purpose of device changes (refer to Section 7.8.3). Relevant data, as specified in the appropriate study plans and specifications, will be transmitted to the sponsor.

8.5 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review according to the Trial Monitoring Plan 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 participant 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, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

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 8.7.

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

8.6 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.

8.7 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

9. ETHICAL CONSIDERATIONS

9.1 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 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 E.U. *Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

9.2 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/IEC 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 their participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a *patient's* willingness to continue in the study, the participant or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC requirements. 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 participant or the participant'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.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, 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 10.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written 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.

9.4 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 participant 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 participant'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 10.6).

9.5 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 4.2).

10. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

10.1 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 participant data, including an audit trail containing a complete record of all changes to data.

10.2 PROTOCOL DEVIATIONS

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

10.3 MANAGEMENT OF STUDY QUALITY

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

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

10.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' 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.

10.5 ADMINISTRATIVE STRUCTURE

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

Approximately 40 sites globally will participate to enroll approximately 400 participants in Cohort A and [redacted] participants in Cohort B. Enrollment will occur through an IxRS.

10.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses, in clinical study 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 9.4 for details), and redacted Clinical Study Reports and*/or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Studies Data 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.

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 studies 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.

10.7 PROTOCOL AMENDMENTS

This study will be conducted in accordance with the protocol and with the following:

- *Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines*
- *Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice*
- *Applicable laws and regulations.*

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- *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*
- *Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures*
- *Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations*

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Appendix 1: Schedule of Activities

Schedule of activities for Cohort A

	Screening (Days -28 to 0)	Baseline [a] (Cycle 1, Day 1)	Treatment period [b]	Post-last treatment safety follow-up visit (28 days) [c]	Follow-up telephone call (90 days) [d]
Approximate visit frequency (as per local standard):					
mNSCLC	Once	Once	~Every 2–4 weeks	Once	Once
ES-SCLC	Once	Once	~Every 3 weeks	Once	Once
HCC	Once	Once	~Every 3 weeks	Once	Once
Informed consent [e]	x				
Diagnosis confirmation [f]	x				
Inclusion/exclusion criteria	x				
Randomization		x *(-3 days)*			
Medical history, participant characteristics, *socioeconomic status,* and demographical data	x				
Cancer treatment history	x				
Documentation of PD-L1-positivity status by local test[x]	*x*				
Concomitant medications/treatments	x		x	x	
Vital signs [g]		x	x	x	
Hematology [h]		x	x	x	
Chemistry [i]		x	x	x	
Coagulation [j]		x	x	x	
Thyroid function testing [k]		x	x	x	
Urinalysis [l]		x	x	x	
Complete physical examination [m]	x				
Limited physical examination [n]			x	x	
Height	x				
Weight [o]	x	x	x		

Appendix 1: Schedule of Activities

	Screening (Days -28 to 0)	Baseline [a] (Cycle 1, Day 1)	Treatment period [b]	Post-last treatment safety follow-up visit (28 days) [c]	Follow-up telephone call (90 days) [d]
Assessment of disease progression [p]		As per local standard of care			
MDASI [q]		x	Weeks 6, 12, 18, 24 *(± 3days)*		x
HRQoL – EORTC IL6 GHS/QoL and EQ-5D-5L [q]		x	Weeks 6, 12, 18, 24 *(±3days)*		x
EORTC OUT-PATSAT7b [q]		x	Week 9 *(±3days)*		x
DPM participant training [r, s]		x			
DPM completion by participant [r]		x [t]	x [u]		
ADEs/SADEs and AEs/SAEs [v]		x	x	x	x
Anti-cancer treatment administration [w]		x	x		
Survival status			x	x	x

ADE =adverse device effect; AE = adverse event; DPM = Digital Patient Monitoring; EQ-5D-5L = EuroQoL 5 Dimension, 5-Level Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; ES-SCLC = extensive-stage small-cell lung carcinoma; GHS = global health status; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life; IL6 = item library 6; m = metastatic; NSCLC = non-small cell lung cancer; OUT-PATSAT7 = out-patient satisfaction with cancer care questionnaire; QoL = Quality of Life scale; SADE =serious adverse device effect; SAE = serious adverse event.

Notes:
- Available data as per SOC will be collected; no additional diagnostic or monitoring procedures shall be requested outside of local routine clinical practice.
- Participant data collection will continue until the end of the follow up period, or until death, loss to follow-up, or withdrawal of consent.

[a] Baseline visit will occur on Cycle 1, Day 1. Baseline assessments should be conducted prior to the administration of anti-cancer treatment. *Laboratory assessments must be performed within 72 hours of first study treatment (Day 1 of Cycle 1).*

[b] Visits for each indication will be repeated as necessary as per SOC. Treatment regimens per indications are outlined in Section 5.1.

[c] Follow-up visit will occur 28 days after the patient discontinues their anti-cancer treatment (i.e., 28 days after the last dose of the last administered component of the regimen, which may or may not be Atezolizumab).

[d] Follow-up telephone call will occur 90 days after the participant receives the last dose of Atezolizumab (IV) treatment or discontinues Atezolizumab treatment.

[e] Informed consent must be documented before any study-specific procedures are performed.

[f] Diagnosis confirmation via histology or radiological report, except for HCC where ultrasound and alpha-fetoprotein (AFP) may be sufficient for diagnosis confirmation and a tissue biopsy may not be required and for mNSCLC or ES-SCLC where cytology may be sufficient for diagnosis.

[g] Vital signs will be carried out locally as per local SOC.

Appendix 1: Schedule of Activities

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). *Only standard of care measurements are required.*

[i] Chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. *Only standard of care measurements are required.*

[j] Coagulation includes INR, aPTT, and PT. *Only standard of care measurements are required.*

[k] Thyroid function testing includes thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4. *Only standard of care measurements are required.*

[l] Urinalysis (pH, specific gravity, glucose, protein, ketones, blood*); dipstick permitted. Only standard of care measurements are required.*

[m] Includes 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.

[n] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[o] Weight is to be measured at Day 1 of each cycle, or whenever the investigator considers there is a substantial change from baseline.

[p] Radiologic confirmation per RECIST is not mandated.

[q] PRO instruments should be conducted by the participant at-home or at the clinic. At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of anti-cancer treatment, unless otherwise specified.

[r] Only for participants randomized to the DPM arm.

[s] Participants randomized to the DPM arm will receive training on use of the DPM solution at the baseline visit. DPM participant training will include setting up an account for the participant.

[t] The participant will complete the baseline assessment of symptoms that occurred over the previous 7 days at the end of the DPM participant training session, under the supervision of the trainer.

[u] Participants can report symptoms in real-time throughout the course of the study using the DPM solution. Participants will receive weekly messages to remind them that they must report symptoms at least every 7 days.

[v] Includes adverse events due to the device and adverse events due to the treatment regimen.

[w] All the above assessments should be conducted before anti-cancer treatment is administered.

[x] *Documented PD-L1 positivity (PD-L1 expression on ≥ 1% of tumor cells) must have been determined locally using a Health-Authority approved immunohistochemistry assay. Documentation of PD-L1-positivity with a full pathology report of the local testing results is required to be submitted to the Sponsor.*

Appendix 1: Schedule of Activities

Schedule of activities for Cohort B

	Screening	Hospital Treatment Period			Disease control and safety visit [cc]	*At-home Treatment Visits* [b]		End of treatment visit [c]	Follow-up telephone call
Cycle		1 [a]	2	3	4 to 15	4 to 16			
Day	-28 to -1	1 (±3 days)			every 12 weeks after the first *at-home* treatment visit (± 5 days)	*7 to 3 days prior to each cycle day 1*	*1 (±3 days) of each 21-day cycle*	≤ 30 days from last study treatment	90 days from last study treatment
Informed consent [d]	x								
Diagnosis confirmation [e]	x								
Inclusion/exclusion criteria	x								
PD-L1 expression and EGFR and ALK mutational status [f]	x								
Medical history, participant characteristics, *socioeconomic status, time required to travel to the site* and demographical data	x								
Cancer treatment history	x								
Concomitant medications/ *treatments*	x	Collected on an ongoing basis							
Vital signs [g]	x	x	x	x	x		x [h]	x	
Weight [i]	x	x	x	x	x			x	

Appendix 1: Schedule of Activities

	Screening	Hospital Treatment Period			Disease control and safety visit [cc]	*At-home Treatment Visits* [b]		End of treatment visit [c]	Follow-up telephone call
Cycle		1 [a]	2	3	4 to 15	4 to 16			
Day	-28 to -1	1 (±3 days)			every 12 weeks after the first *at-home* treatment visit (± 5 days)	*7 to 3 days prior to each cycle day 1*	*1 (±3 days) of each 21-day cycle*	≤ 30 days from last study treatment	90 days from last study treatment
Height	x				x				
Complete physical examination [j]	x								
Limited physical examination [k]		x	x	x	x		x [h]	x	
ECOG Performance Status	x	x		x	x			x	
Hematology [l]	x	x	x	x	x	x [h]		x	
Chemistry [m]	x	x	x	x	x	x [h]		x	
Coagulation [n]	x	x			x			x	
Thyroid function testing [o]	x	x			x	x [h]		x	
Urinalysis [p]	x	x							
HIV/HBV/HCV Serology [bb]	*x*								
Pregnancy test [q]	x	x	x	x	x		x [h]	x	(x) [r]
Phone/Video HCP contact [s]							x		
MDASI [t]		x		x			*x (Cycles 6, 9, and 12)*	x	

Appendix 1: Schedule of Activities

	Screening	Hospital Treatment Period			Disease control and safety visit [cc]	*At-home Treatment Visits* [b]		End of treatment visit [c]	Follow-up telephone call
Cycle		1 [a]	2	3	4 to 15	4 to 16			
Day	-28 to -1	1 (±3 days)			every 12 weeks after the first *at-home* treatment visit (± 5 days)	*7 to 3 days prior to each cycle day 1*	*1 (±3 days) of each 21-day cycle*	≤ 30 days from last study treatment	90 days from last study treatment
HRQoL – EORTC IL6 GHS/QoL,EQ-5D-5L, [t]		x		x			*x (Cycles 6, 9, and 12)*	x	
Participant acceptability questionnaire [t]							*x (Cycles 4, 6, and 8)*	x	
DPM *patient* training [u]		x							
DPM completion by *patient*		x [v]	x [w]						
ADEs/SADEs and AEs/SAEs [x]		Collected on an ongoing basis							x
Atezolizumab SC administration [y]		x	x	x			x [h]		
Tumor assessment	x [z]	x [aa]							

ADE = adverse device effect; AE = adverse event; DPM = Digital Patient Monitoring; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQoL 5 Dimension, 5-Level Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; GHS = Global Health Score; HCP = Healthcare Professional; HRQoL = health-related quality of life; IL6 = item library 6; IRR = injection related reaction; MDASI = MD Anderson Symptom Interference; NSCLC = non-small cell lung cancer; OUT-PATSAT7 = out-patient satisfaction with cancer care questionnaire; PRO = *patient*-reported outcome; QoL = quality of life; SADE = serious adverse device effect; SAE = serious adverse event; SC = subcutaneous; IL6 = EORTC Global Health Status/Quality of Life scale

Appendix 1: Schedule of Activities

[a] Baseline visit will occur on Cycle 1, Day 1. Baseline assessments should be conducted prior to the administration of Atezolizumab SC. *Laboratory assessments must be performed within 72 hours of first study treatment (Day 1 of Cycle 1).*

[b] For participants who develop IRRs (or symptoms suggestive of IRR that require immediate medical intervention during infusion) during the first three cycles of Atezolizumab SC administration *or that stop to receive the treatment at-home for any other reason*, all subsequent Atezolizumab SC administration will be done in the hospital setting only. For low grade (Grade 1–2) IRR events during the first three cycles, administration in the *at-home treatment* setting may be considered with premedication.

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

[d] Informed consent must be documented before any study-specific procedures are performed.

[e] Participants must have a complete resection of a histologically or cytologically confirmed Stage IIB-IIIB (T3-N2) NSCLC (per the UICC/AJCC staging system, 8th edition; Detterbeck et al. 2018). Participants must have completed adjuvant chemotherapy at least 4 weeks and up to 12 weeks prior to randomization and must be adequately recovered from chemotherapy treatment.

[f] Results of PD-L1 expression tests and EGFR and ALK mutational status performed prior to obtaining informed consent and within 28 days prior to may be used for screening assessments rather than repeating such tests, providing that these tests meet protocol requirements.

[g] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. See Section 5.5.4.2 for details of the timings of vital sign assessments.

[h] *Samples will be collected by a qualified mobile HCP within 3 to 7 days prior to treatment administration and sent to the central laboratory for analysis. This is not required if there are valid local laboratory results available for that time window. Central laboratory results will be shared with the investigator prior to each planned drug administration at-home.*

[i] Weight is to be measured at Day 1 of each cycle, or whenever the investigator considers there is a substantial change from baseline.

[j] Includes 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.

[k] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. In the *at-home treatment* setting findings are to be reported to the study site.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). *Assessments to be performed by the local laboratory in the hospital setting and central laboratory during the treatment at-home phase.*

[m] Chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. *Assessments to be performed by the local laboratory in the hospital setting and central laboratory during the treatment at-home phase.*

[n] Coagulation includes INR, aPTT, and PT.

[o] Thyroid function testing includes thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4.

Appendix 1: Schedule of Activities

[p] Urinalysis (pH, specific gravity, glucose, protein, ketones, blood*); dipstick permitted.*

[q] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study Atezolizumab SC. Urine pregnancy tests (or serum, if urine is not feasible) will be performed at specified subsequent visits during treatment, at the treatment discontinuation visit, and may be required beyond Atezolizumab SC discontinuation, monthly for 5 months after the final dose of Atezolizumab SC. Pregnancy tests after Atezolizumab SC discontinuation can be performed at-home. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] In accordance with country-specific health authority mandates, pregnancy tests may be required beyond treatment discontinuation, monthly for 5 months after the final dose of Atezolizumab. Pregnancy tests after study treatment discontinuation can be performed at-home. If a home urine pregnancy test is positive, it must be confirmed by a serum pregnancy test and if confirmed, immediately communicated to the treating physician.

[s] During Atezolizumab SC administration in the *at-home treatment* setting, a phone or video connection between the qualified mobile HCP and the treating clinic HCPs will be established.

[t] PRO instruments should be conducted by the participant at-home or at the clinic. MDASI, EORTC IL6 GHS/QoL, EQ-5D-5L, and EORTC OUT-PATSAT7 will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of Atezolizumab SC, unless otherwise specified. The participant acceptability questionnaire will be administered following treatment administration.

[u] Participants will receive training on use of the DPM solution at the baseline visit. DPM participant training will include setting up an account for the participant.

[v] The participant will complete the baseline assessment of symptoms that occurred over the previous 7 days at the end of the DPM participant training session, under the supervision of the trainer.

[w] Participants can report symptoms in real-time throughout the course of the study using the DPM solution. Participants will receive weekly messages to remind them that they must report symptoms at least every 7 days as well as 24 hours after each Atezolizumab SC administration in the *at-home treatment* setting.

[x] Includes adverse events due to the device and adverse events due to the treatment regimen.

[y] All the above assessments should be conducted before Atezolizumab SC is administered.

[z] 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, so long as they meet criteria outlined in Section 5.5.5. Screening assessments must include CT scans with contrast or MRI scans of the chest, abdomen, pelvis, and brain. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in participants with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and brain should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all participants (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease may be used.

Appendix 1: Schedule of Activities

[aa] *Patient*s will undergo tumor assessments as per local standard of care.

[bb] *HIV serology, HBV serology (HBsAg, HBsAb, and total HBcAb for all patients; HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test), HCV serology (HCV antibody for all patients; HCV RNA for patients with a positive HCV antibody test)*

[cc] *Disease control visits are site visits and only take place while the patient is in the at-home treatment setting. If the patient receives the study drug administrations in the hospital, no disease control visits are required. Local laboratory results from the disease control visits can be used to confirm the next study drug administration.*

Appendix 2
Eastern Cooperative Oncology Group Performance Status Scale

GRADE	PERFORMANCE STATUS - WHO CLASSIFICATION
0	Fully active, able to carry out all normal activity 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 more than 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed and chair

Appendix 3
Selected PRO-CTCAE and Other Symptoms

Category	Symptom / AE	PRO CTCAE term	Cohort A: mNSCLC/ ES-SCLC	Cohort B: eNSCLC	Cohort A: HCC
Sleep/Wake	Fatigue / Tiredness / Asthenia	53. PRO-CTCAE™ Symptom Term: Fatigue	X	X	X
Pain	Abdominal pain	17. PRO-CTCAE™ Symptom Term: Abdominal pain	X	X	X
Pain	Chest Pain	N/A	X	X	
Pain	Headache	49. PRO-CTCAE™ Symptom Term: Headache	X	X	
Pain	Musculoskeletal pain, bone/joint pain	51. PRO-CTCAE™ Symptom Term: Joint pain	X	X	X
Respiratory	Cough	20. PRO-CTCAE™ Symptom Term: Cough	X	X	
Respiratory	Shortness of breath (Dyspnea)	19. PRO-CTCAE™ Symptom Term: Shortness of breath	X	X	
Cardiologic	Pounding or Racing Heartbeat (Palpitations)	23. PRO-CTCAE™ Symptom Term: Heart palpitations	X	X	
Cardiologic	Swelling of arms and legs	22. PRO-CTCAE™ Symptom Term: Swelling		X	X
Cutaneous	Itching (Pruritus)	28. PRO-CTCAE™ Symptom Term: Itching	X	X (alert for any increase)	X
Cutaneous	Rash, Urticaria	24. PRO-CTCAE™ Symptom Term: Rash	X	X (alert for any increase)	X
Cutaneous	Infusion or injection site reaction	79. PRO-CTCAE™ Symptom Term: Pain, redness, inflammation, rash or swelling at injection site'	X	X (alert for any increase)	
Gastrointestinal	Decreased appetite (Anorexia)	8. PRO-CTCAE™ Symptom Term: Decreased appetite	X	X	X
Gastrointestinal	Diarrhea	16. PRO-CTCAE™ Symptom Term: Diarrhea	X	X	X
Gastrointestinal	Nausea	9. PRO-CTCAE™ Symptom Term: Nausea	X	X	X
Gastrointestinal	Vomiting	10. PRO-CTCAE™ Symptom Term: Vomiting	X	X	
Gastrointestinal	Constipation	15. PRO-CTCAE™ Symptom Term: Constipation			X
Gastrointestinal	Taste Changes (e.g., bad taste in mouth)	7. PRO-CTCAE™ Symptom Term: Taste changes	x	x	
Mood	Cognitive or psychological (anxiety, fear, depression)	54. PRO-CTCAE™ Symptom Term: Anxious	x	x	
Neurological	Peripheral neuropathy	39. PRO-CTCAE™ Symptom Term: Numbness & tingling	x	x	
Miscellaneous	Fever	N/A	x	x	x

Appendix 3: Selected PRO-CTCAE and other Symptoms

Miscellaneous	Haemorrhage / Bleeds (blood in urine, nose bleed, blood in cough)	N/A	x	x	x
Miscellaneous	Weight loss	N/A	x	x	x
Other symptoms	*Other symptoms (free text field)*	N/A	*x*	*x*	x

AE = adverse event; ESSCLC = ES-SCLC = extensive-stage small-cell lung carcinoma; HCC = hepatocellular carcinoma; mNSCLC = metastatic non-small cell lung cancer; N/A = not applicable; PRO CTCAE = patient-reported outcomes common terminology criteria for adverse Events;

Appendix 4
Participant Acceptability Questionnaire

You previously received Atezolizumab delivered through subcutaneous (SC) injection at a clinic, and have now received Atezolizumab through SC injection at-home.

We are interested in understanding your experiences and preferences as they relate to SC administration of Atezolizumab treatment in the clinic versus treatment at-home.

Please answer the following questions about your experience. There are no right or wrong answers.

1. Were you satisfied with the care you received at-home?

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

2. Would you describe the type care you received as convenient?

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

3. Did you prefer to receive your treatment in the clinic or at-home?
   In the clinic At-home No preference *(Go to question 6)*

4. If you have a preference for one of the locations, how strong is this preference?
   Very strong Fairly strong Not very strong

5. If you have a preference for one of the locations, what are the TWO main reasons for your preference?

   □ Feels less emotionally distressing
   □ Reduces my risk of infection
   □ Provides more time to interact with a health care provider
   □ It's generally more convenient
   □ Other reason; please specify:

6. Please use the space below for any other comments you would like to add:

Appendix 4: Participant Acceptability Questionnaire

7. During my treatment at-home I felt supported by the treatment team

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

8. The nurses were very well informed about my history and current medical condition and treatment

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

9. I always knew who was responsible for my treatment and care

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

10. There was always qualified staff available if I had questions

Strongly disagree Somewhat disagree Somewhat agree Strongly agree

Appendix 5
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune *myelitis* • *Autoimmune* myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn's disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • *G*ranulomatosis *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 anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 6
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 administration in a clinical setting:

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

In the at-home treatment setting, emergency medical services are to be called immediately and the provided rescue medication (epinephrine) is to be used as applicable to stabilize the patient until emergency medical services arrive.

PROCEDURES

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

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway *(as applicable).*
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible. *In the treatment at-home setting this will be provided by the emergency medical services.*
5. Administer *epinephrine (*antihistamines or other medications and IV fluids *in the hospital setting)* as required by participant status and as directed by the physician in charge.
6. Continue to observe the *patient* and document observations.

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

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

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

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

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, Atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding Atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold Atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before Atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of Atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit–risk balance for a given *patient* prior to further administration of Atezolizumab. -*R*esumption of Atezolizumab may be

considered *in patients who are* deriving benefit and ha*ve* fully recovered from the immune–mediated event. The decision to re-challenge *patients* with Atezolizumab should be based on the investigator's assessment of *the benefits and risks* and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in participants 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 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.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue Atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider *patient* referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding Atezolizumab.
Pulmonary event, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer *patient* to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • 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 or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact the Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

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

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

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

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

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

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

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.

Table 2 Management Guidelines for Hepatic Events (cont.)

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

LFT = liver function test.

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

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

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

GASTROINTESTINAL EVENTS

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

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

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

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

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 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 participant 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 *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.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. *Patients* should be referred to an endocrinologist if an endocrinopathy is suspected. TSH and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue Atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding Atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider *patient* referral to endocrinologist. • Resume Atezolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• *Withhold Atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Refer to an endocrinologist.* • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • *Resume Atezolizumab when symptoms are controlled and thyroid function is improving.* • *Permanently discontinue Atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue Atezolizumab. • Monitor TSH every 4 weeks. • Consider participant referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider participant referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding Atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider participant referral to endocrinologist. • Resume Atezolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	• *Withhold Atezolizumab.* • *Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.* • *Refer to 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 participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with Atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer participant 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 participant is stable on replacement therapy, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better or participant is not stable on replacement therapy while withholding Atezolizumab, permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue Atezolizumab. • Investigate for diabetes. If participant has Type 1 diabetes, treat as a Grade 3 event. If participant does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold Atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume Atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging.

[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 participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with Atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging.

[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 participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants 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 participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with Atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

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

All *patient*s with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

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

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

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

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

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

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

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

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of Atezolizumab. However, participants 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 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 interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a participant 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 participants 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 as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize *patient* (monitoring in the ICU is recommended), permanently discontinue Atezolizumab, and contact *the* Medical Monitor. [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, nonrebreather mask, or Venturi-mask	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize participant until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit *patient* to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for *patients* who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit *patient* to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For *patients* who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize *patient* until complete resolution of symptoms.

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

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

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

[a] Grading system for these management guidelines is based on ASTCT Consensus Grading 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 *medication*s, 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 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. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretic *medication*s, 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* 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.)

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 participant 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* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10*, with specific guidelines for myelitis provided in Table 11*.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue Atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer *patient* to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy* – If event resolves to Grade 1 or better, resume Atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume Atezolizumab* [b] – *If event does not resolve fully while withholding Atezolizumab, permanently discontinue Atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c] • Refer *patient* to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c] • Refer *patient* to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

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

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

Table 11 Management Guidelines for Immune-Mediated Myelitis

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue Atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue Atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue Atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

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

Table 12 Management Guidelines for Immune-Mediated Meningocephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor.[a] • 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 participants must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. *Patients* with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table13 .

Table 13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue Atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer *patient* to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [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), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients* with possible myositis should be referred to a rheumatologist or neurologist. *Patients* with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the below 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 (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold Atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer *patient* to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue Atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. [c] • Refer *patient* to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* 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.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

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

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile participant should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (> 684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L ($\leq 181{,}000/\mu$L)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (> 156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (≤ 360 mg/dL)

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

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue Atezolizumab and contact *the* Medical Monitor. • Consider *patient* referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 8
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab SC (RO5541267)	IMP (test product) [a]	Unauthorized	No [b]
Atezolizumab IV (RO5541267)	*NIMP (other)*	*Authorized*	*Yes*
Bevacizumab (RO4876646)	*NIMP (other)*	*Authorized*	*Yes*
Carboplatin	*NIMP (other)*	*Authorized*	*Yes*
Nab-paclitaxel	*NIMP (other)*	*Authorized*	*Yes*
Epinephrine	*NIMP (other)*	*Authorized*	*Yes*

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

[a] Atezolizumab SC is considered to be an IMP test product in Cohort B.

[b] Atezolizumab IV is approved within the EEA. Atezolizumab is used in a different form from the marketing authorization.

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