Official Title: An Open-Label, Multicenter, Phase II Study to Evaluate the Therapeutic Activity of Simlukafusp Alfa (RO6874281), an Immunocytokine, Consisting of Interleukin-2 Variant (IL-2v) Targeting Fibroblast Activation Protein-A (FAP), in Combination With Atezolizumab (Anti-PD-L1), Administered Intravenously, in Participants With Advanced and/or Metastatic Solid Tumors

NCT Number: NCT03386721

Document Date: Protocol version 10: 21-December-2020

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE II STUDY TO EVALUATE THE THERAPEUTIC ACTIVITY OF SIMLUKAFUSP ALFA (RO6874281), AN IMMUNOCYTOKINE, CONSISTING OF INTERLEUKIN-2 VARIANT (IL-2V) TARGETING FIBROBLAST ACTIVATION PROTEIN-A (FAP), IN COMBINATION WITH ATEZOLIZUMAB (ANTI-PD-L1), ADMINISTERED INTRAVENOUSLY, IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	BP40234
VERSION:	10
EUDRACT NUMBER:	2017-003182-94
IND NUMBER:	138617
TEST PRODUCTS:	Simlukafusp alfa (RO6874281)/Atezolizumab (Tecentriq®)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 21 September 2017 Version 2: 16 October 2017 Version 3: 20 October 2017 Version 4: 09 May 2018 Version 5: 20 August 2018 Version 6: 29 March 2019 Version 7: 08 April 2019 Version 8: 16 December 2019 Version 9: 25 June 2020
DATE AMENDED:	Version 10: See electronic date stamp below

Date and Time (UTC)	Title	Approver's Name
21-Dec-2020 09:33:17	Company Signatory	[redacted]

FINAL PROTOCOL APPROVAL

CONFIDENTIAL

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE II STUDY TO EVALUATE THE THERAPEUTIC ACTIVITY OF SIMLUKAFUSP ALFA (RO6874281), AN IMMUNOCYTOKINE, CONSISTING OF INTERLEUKIN-2 VARIANT (IL-2V) TARGETING FIBROBLAST ACTIVATION PROTEIN-A (FAP), IN COMBINATION WITH ATEZOLIZUMAB (ANTI-PD-L1), ADMINISTERED INTRAVENOUSLY, IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
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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 keep the signed original form in your study files, and return a copy to your local Study Monitor.

PROTOCOL AMENDMENT, VERSION 10: RATIONALE

Protocol BP40234 version 9 has been amended and changes to the protocol, along with a rationale for each change, are summarized below.

Main changes

In accordance with the latest version of the Investigator's Brochure for atezolizumab, the following sections have been updated:

- Section 8.3.8.2: Severe cutaneous adverse reactions added as a risk associated with atezolizumab.
- Section 8.3.6: Events suggestive of hemophagocytic lymphohistiocytosis or macrophage activation syndrome have been added to the list of non-serious adverse events of special interest.
- Appendix 9: Update of the management guidelines for infusion-related reactions (including cytokine release syndrome), dermatologic events, and hemophagocytic lymphohistiocytosis and macrophage activation syndrome.
- Appendix 10: The ASTCT (American Society for Transplantation and Cellular Therapy) cytokine release syndrome consensus grading scheme has been included.

Additional Changes

- RO6874281 has been replaced by simlukafusp alfa, the international nonproprietary name, throughout the protocol.
- Section 1.3: Physical examinations requirements from Cycle 5 onwards have been adapted to Day 1 schedule of Cycles 1 to 4. Consequently, the physical examination will be performed before treatment; the post-dose examination on Day 1 has been removed from the schedule.
- Section 1.3: PD Sample (FACS) Basic, PD Sample (Plasma), "PD Sample (Serum) at 24, 36, 48, 60, 72, 84, and 96 weeks after Cycle 1 Day 1 and PD Sample (FACS) Advanced at 24, 48, and 96 weeks after Cycle 1 Day 1 will no longer be collected in all cohorts irrespective of the treatment regimens, i.e., Q3W and QW/Q2W. With the PD samples collected up to date, there is sufficient data available to answer the PD sample associated secondary objectives "treatment-induced PD effects on peripheral blood lymphocytes, soluble markers, and tumor microenvironment".
- Sections 1.3 and 8.6.2: During the further conduct of the study, the collection of the on-treatment biopsy scheduled on Cycle 2 Day 8 and Cycle 3 Day 8 for the Q3W and the QW/Q2W schedule, respectively, may be regarded as optional for patients enrolled in Part III. A sufficient number of paired fresh biopsies have been collected in the simlukafusp alfa plus atezolizumab combination treatment cohorts in the Squamous Cell Carcinoma patient population (Part III) to answer the associated secondary objectives "treatment-induced PD effects in tumor samples" to make the previous mandatory on-treatment biopsies optional.

- Sections 2.1, 2.3, and 4.3.1: Minor additions were made to the rationale and benefit/risk assessment sections.
- Sections 4.1.5 and 7.2: A treatment cap of 24 months has been added. However, in case the participant has reached the defined duration and continues to derive benefit, a longer treatment duration might be granted by the Sponsor.
- Section 8.2: Text in relation to COVID-19 has been added.
- Section 8.3.9: Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis has been added to Table 17.

Minor Changes

- Sections 6.2 and 8.3.8.2: Text has been deleted where there is duplication of information.

Additional minor changes have been made to improve clarity and consistency. New information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
A	atezolizumab
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
BAL	bronchoalveolar lavage
C	Cycle
C_{max}	maximum concentration
C_{trough}	minimum concentration
Chem	blood chemistry
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLS	capillary leak syndrome
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
Coag	coagulation
COPD	chronic obstructive pulmonary disease
CPI	checkpoint inhibitor
CR	complete response
CRCL	creatinine clearance
CRP	C-reactive protein
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCR	disease control rate
Discon	Discontinuation Visit
DLT	dose-limiting toxicities
DoR	duration of response
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked, immunosorbent assay
EOI	End of Infusion
ESMO	European Society for Medical Oncology
F	FAP-IL2v (*simlukafusp alfa*)
F/U	follow up
FACS	fluorescence-activated cell sorting
FAP	fibroblast activation protein α
FAP-IL2v	*simlukafusp alfa*
FDA	U.S. Food and Drug Administration
FEV	forced expiratory volume
FFPE	formalin-fixed, paraffin-embedded
FVC	forced vital capacity
gem	gemcitabine
GGT	gamma-glutamyl transferase
GI	gastrointestinal
H	Hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hema	hematology
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papilloma virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	Independent centralized review
IFN	interferon
IFN-α	interferon-alpha
IFN-β	interferon-beta
IFN-γ	interferon-gamma
IHC	Immunohistochemistry
Ig	immunoglobulin
IgE	immunoglobulin E
IL	interleukin

Abbreviation	Definition
IL-2R	interleukin-2 receptor
IL-2v	interleukin 2 variant
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
iRECIST	modified RECIST for immune-based therapies
IRR	infusion/injection-related reaction
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
JMC	Joint Monitoring Committee
KIR	killer cell immunoglobulin-like receptor
KPS	Karnofsky Performance Score
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LPLV	last participant's last visit
min	minute
mPFS	median progression-free survival
MMR	mismatch repair genes
mRECIST	modified RECIST
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum-tolerated dose
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
NPC	nasopharyngeal carcinoma
NSCLC	non−small-cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation	Definition
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor
QW	once weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
R	randomization
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SI	International System of Units
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard of care
T_{reg}	regulatory T cell
TA	tumor assessment
TEM	memory T cell
TGK	tumor growth kinetic
TMB	tumor mutation burden
TMDD	target-mediated drug disposition
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TNM	tumor-node-metastasis
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
V	volume of distribution
VAD	ventricular assist device
VEGF	vascular endothelial growth factor
vin	vinorelbine
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL, MULTICENTER, PHASE II STUDY TO EVALUATE THE THERAPEUTIC ACTIVITY OF SIMLUKAFUSP ALFA (RO6874281), AN IMMUNOCYTOKINE, CONSISTING OF INTERLEUKIN-2 VARIANT (IL-2V) TARGETING FIBROBLAST ACTIVATION PROTEIN-A (FAP), IN COMBINATION WITH ATEZOLIZUMAB (ANTI-PD-L1), ADMINISTERED INTRAVENOUSLY, IN PARTICIPANTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS**
PROTOCOL NUMBER:	BP40234
VERSION:	10
TEST PRODUCT:	RO6874281/atezolizumab
PHASE:	II

RATIONALE

This Phase II study of *simlukafusp alfa*, in combination with atezolizumab in participants with advanced and/or metastatic solid tumors is designed to confirm the hypothesis that immune cell activation by *simlukafusp alfa* improves clinical activity of atezolizumab.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate antitumor activity of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in comparison with the SoC in participants with advanced/and or metastatic solid tumors	• ORR according to RECIST v1.1
Secondary	
• To further characterize the antitumor activity of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in participants with advanced/and or metastatic solid tumors relative to SoC.	• DCR • DoR • PFS • OS, if data are mature at the time of analysis [a]
• To evaluate the safety and tolerability of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs	• Incidence of and severity of AEs • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results
• To determine the relevance of the baseline tumor PD-L1 status for treatment benefit	• PD-L1 status by immunohistochemical methods

Objectives	Endpoints
• To characterize in tumor samples treatment-induced PD effects of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs	• Change from baseline in density (cell/mm^2) of CD8+ and CD3-perforin+ cells, and PD-L1 by immunohistochemical methods

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; FAP = fibroblast activation protein-α; PD = pharmacodynamic; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors; SoC = standard of care.

[a] For Part I Cohort D, OS will not be analyzed due to crossover.

OVERALL DESIGN

Study Design

This is an open-label, multicenter, basket trial Phase II, clinical study to evaluate the antitumor activity of *simlukafusp alfa* in combination with atezolizumab over a range of advanced and/or metastatic solid tumors. This study is adaptive in nature, and is a multiple-part study.

simlukafusp alfa in combination with atezolizumab may deliver improved clinical benefit for participants as compared with checkpoint inhibition monotherapy. Checkpoint inhibition therapy is also being explored in combination with other drugs. While *simlukafusp alfa* + atezolizumab is the backbone investigated in this basket trial, *simlukafusp alfa* has the potential of being combined with other partners. On the basis of data from ongoing combination studies of *simlukafusp alfa* and atezolizumab, additional combination therapies (*simlukafusp alfa* + atezolizumab + drug X) may be proposed and added to this study protocol via an amendment.

There are currently two treatment schedules in the protocol:

- Once weekly (QW)/every 2 weeks (Q2W) schedule (induction/maintenance): *simlukafusp alfa* QW + atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* + atezolizumab Q2W, thereafter
- Every 3 weeks (Q3W) schedule: *simlukafusp alfa* + atezolizumab Q3W

For all cohorts, the actual number of participants enrolled may be increased to ensure that the necessary numbers of response-evaluable participants presented below are obtained.

Part I

In Part I, approximately 220 response-evaluable participants with advanced and/or metastatic non−small cell lung cancer (NSCLC) after at least one previous regimen of anticancer therapy for metastatic disease will be divided into the following cohorts:

- Cohort A: Checkpoint inhibitor (CPI) naïve participants (20 response-evaluable participants), optional biopsies
- Cohort B: CPI-experienced participants (20 response-evaluable participants), mandatory biopsies
- Cohort C: Contingent upon the confirmation of the treatment's safety and preliminary activity analysis, a mandatory biopsy cohort may be introduced to enroll 20 response-evaluable CPI-naïve NSCLC participants.
- Cohort D: Contingent upon the confirmation of the treatment's safety and preliminary activity analysis of Cohort B, a cohort may be opened to enroll 120 randomized CPI-experienced participants. Participants in Cohort D must have additionally experienced disease progression after or during docetaxel therapy; biopsies are mandatory
- Cohort F: CPI-experienced participants; platinum pre-treated (40 response-evaluable participants), mandatory biopsies

Participants in Cohorts A, B, and C will follow the QW/Q2W treatment schedule.

Participants in Cohort D will be randomized into three arms, as follows:

- Arm 1: *simlukafusp alfa* in combination with atezolizumab; QW/Q2W schedule
- Arm 2: *simlukafusp alfa* in combination with atezolizumab; Q3W schedule
- Arm 3: Control arm; single-agent chemotherapy with gemcitabine or vinorelbine

Participants in Arm 3 who experienced disease progression during or after platinum + gemcitabine doublet chemotherapy in an earlier treatment line will receive vinorelbine; all other participants in Arm 3 will receive gemcitabine. The choice between gemcitabine and vinorelbine will be made before the randomization takes place. There is paucity of clinical activity data of CPI treatment after previous exposure to a compound of the same drug class. Activity data from Arm 3 will allow interpreting the signals of Arm 1 and Arm 2 more robustly and increases the scientific value of the study.

Participants in Cohort D who are randomized to Arm 3 and who progress on chemotherapy treatment have the opportunity to crossover to Arm 1 or Arm 2 and receive *simlukafusp alfa* in combination with atezolizumab (QW/Q2W or Q3W). The decision to crossover is at the discretion of the investigator. Participants must have documented radiographic (or other imaging-based assessment) disease progression reported in the electronic case report form (eCRF). The Sponsor's approval based on the provided tumor assessment data is needed prior to crossover.

Participants in Cohort F will follow the Q3W treatment schedule.

Part II

In Part II, up to 80 response-evaluable participants with previously untreated driver-mutation negative advanced and/or metastatic NSCLC will be included. Participants must not have been exposed to any prior regimen of anticancer therapy (i.e., chemotherapy, mutation-targeted therapy and/or CPI therapy). Part II will consist of one cohort (Cohort E). This cohort will include only PD-L1 high participants (tumor proportion score [TPS] $\geq$ 50%, used interchangeably with tumor cell [TC] staining). Eligible participants will be randomized to either receive *simlukafusp alfa* QW/Q2W or Q3W in combination with atezolizumab Q2W or Q3W, respectively (see also Figure 2). Participants in Part II are required to provide a mandatory archival tumor tissue sample within 2 months after enrollment.

Part III

In Part III, approximately 160 response-evaluable participants with locally advanced or persistent or relapsed/recurrent and/or metastatic squamous cell carcinoma (SCC) will be divided into the following cohorts:

- Cohort G: CPI-naïve SCC of the head and neck (SCCHN) (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort H: CPI-experienced SCC of the head and neck (SCCHN) (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort I: Previously treated, CPI-naïve squamous esophageal cancer (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort J: Previously treated, CPI-naïve squamous cervical cancer (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsy
- Cohort K: CPI-naïve SCCHN (20 response-evaluable participants), QW/Q2W schedule, 1L/1L+, mandatory *pre-treatment* biopsies
- Cohort L: CPI-experienced SCCHN participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies

- Cohort M: Esophageal SCC participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies.
- Cohort N: Cervical SCC participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies

In Part III, participants in Cohorts G-J will receive *simlukafusp alfa* Q3W in combination with atezolizumab Q3W and participants in Cohorts K-N will receive *simlukafusp alfa* QW in combination with atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* in combination with atezolizumab Q2W.

Length of Study

The recruitment is expected to last approximately 19 months for Part I, approximately 8 months for Part II, and approximately 18 months for Part III of the study.

Participants may continue study treatment for a maximum of 24 months. In case the participant has reached the defined duration and continues to derive benefit, a longer treatment duration might be granted by the Sponsor.

End of Study

The end of the study is defined as the last participant's last visit per protocol (LPLV) (includes the follow-up visits at 28 days and 3 months after the last dose of any study drug, and 120 days after the last dose of atezolizumab, whichever occurs last) or the date at which the last data point from the last participant required for statistical analysis is received (Last Participant, Last Observation), whichever is the latest date, unless the participant was prematurely discontinued.

PARTICIPANT POPULATION

Part I: Participants with advanced and/or metastatic solid tumors after at least one previous regimen of anticancer therapy for metastatic disease. Part II: Participants with advanced and/or metastatic solid tumors with previously untreated driver-mutation negative advanced and/or metastatic NSCLC. *Part III: Participants with locally advanced or persistent or relapsed/recurrent and/or metastatic squamous cell carcinoma (SCC).*

Key Inclusion Criteria

1. Signed informed consent
2. Age ≥ 18 years
3. Measurable disease, as defined by RECIST v1.1
4. ECOG Performance Status 0 or 1 or Karnofsky Performance Score ≥ 70
5. Life expectancy of ≥ 12 weeks
6. Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system [CNS] metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
7. Confirmed at least one tumor lesion with location accessible to safely biopsy per clinical judgment of the treating physician and the participant's consented willingness to undergo baseline and on-treatment tumor biopsies for pharmacodynamics (PD) biomarker analysis (not applicable to Part I Cohort A):

   Previously irradiated lesions should not be counted as target lesions.

   Lesions that are intended to be biopsied should not be counted as target lesions.

   Note: Biopsies are not applicable to participants in Cohorts G, H, K, and L presenting with a single target lesion and absence of any non-target lesion.

   Other exceptions may apply and require discussion and agreement between the Investigator and the Sponsor.
8. Consent to provide an archival tumor tissue sample

Specific Inclusion Criteria for Participants in Part I:

16. Advanced or metastatic NSCLC patients who have failed at least one previous regimen of anticancer therapy
17. Tumors with a known sensitizing mutation (e.g., EGFR, ALK, ROS rearrangement, BRAF V600E mutation) must have experienced disease progression (during or after treatment) or intolerance to treatment with all available standard-of-care (SOC) targeted therapies, respectively

Cohort A: Checkpoint Inhibitor Naïve NSCLC Participants:

18. Participants must have progressed on at least one previous systemic therapy for advanced or metastatic NSCLC disease

Cohort B: Checkpoint Inhibitor Experienced NSCLC Participants:

19. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

Cohort C: Checkpoint Inhibitor Naïve Participants:

20. Participants must have progressed on at least one previous systemic therapy for advanced or metastatic NSCLC disease
21. Participants must have accessible tumor lesions that can be safely biopsied

Cohort D: Checkpoint Inhibitor Experienced Participants:

22. Participants who experienced disease progression during or following treatment with a platinum-containing regimen and a checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy

    Participants should have experienced disease progression on docetaxel therapy.

23. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

Cohort F: Checkpoint-Inhibitor Experienced, Platinum Experienced, Docetaxel-Naïve NSCLC Participants:

24. Participants who experienced disease progression during or following treatment with a platinum-containing regimen and a CPI, given in combination as one line of therapy or as two separate lines of therapy
25. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

Specific Inclusion Criteria for Participants in Part II:

26. Previously untreated NSCLC without sensitizing mutation with available targeted therapy as standard-of-care (SoC)

Cohort E: Participants with High-Tumor PD-L1 Expression:

27. Participants with a PD-L1 TPS ≥50%, who have not received any prior systemic therapy for metastatic NSCLC

Specific Inclusion Criteria for Participants in Part III

28. All participants must have accessible tumor lesions that can be safely biopsied

    Biopsies are not applicable to participants in Cohorts G, H, K, and L presenting with a single target lesion and absence of any non-target lesion.

Cohorts G & K: CPI-Naïve SCCHN Participants

29. Confirmed diagnosis of recurrent or metastatic SCCHN

Cohorts H & L: CPI-Experienced SCCHN Participants

30. Confirmed diagnosis of recurrent or metastatic SCCHN
31. Prior CPI-containing treatment for recurrent or metastatic disease.
32. Experienced progression or intolerance while receiving ≤ 2 line(s) of standard therapy
33. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved).

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

Cohorts I & M: Esophageal Squamous Cell Carcinoma

34. Confirmed diagnosis of recurrent or metastatic esophageal cancer
35. Experienced progression or intolerance while receiving ≥ 1 line of standard therapy

Cohorts J & N: Cervical Squamous Cell Carcinoma

36. Confirmed diagnosis of metastatic, persistent, or recurrent squamous cervical cancer
37. Experienced progression or intolerance while receiving ≥ 1 line of standard therapy

Key Exclusion Criteria

1. Symptomatic or untreated CNS metastases.
2. History of treated asymptomatic CNS metastases with any of the following criteria:
   a. Metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
   b. History of intracranial hemorrhage or spinal cord hemorrhage
   c. Lacking radiographic demonstration of improvement upon the completion of CNS-directed therapy and evidence of interim progression between the completion of CNS-directed therapy and the baseline radiographic study
   d. Ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dosage are allowed.
   e. Stereotactic radiation or whole-brain radiation within 28 days before study treatment administration.
   f. Last CNS radiographic study <4 weeks since completion of radiotherapy and <2 weeks since discontinuation of corticosteroids.

g. CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days before study treatment administration.

3. 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 before enrollment
4. Leptomeningeal disease
13. Dementia or altered mental status that would prohibit informed consent
14. History of, active or suspicion of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

    Participants with a history of autoimmune hypothyroidism on a stable dosage of thyroid replacement hormone may be eligible with approval by the Medical Monitor.

    Participants with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study with approval by the Medical Monitor.
15. History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
16. Bilateral pleural effusion confirmed by x-ray
17. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug
18. Concurrent therapy with any other investigational drug (defined as a treatment for which there is currently no regulatory authority-approved indication)
19. Immunomodulating agents:
    a. Last dose with any of the following agents, for example, etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents) < 28 days before study treatment administration.
    b. Previous immunotherapies including, but not limited to, any cytokine therapies, particularly interleukin-2 and interleukin-2 conjugates, interferon (IFN)-α, IFN-β
    c. Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease)
20. Treatment with systemic immunosuppressive medications including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents within 2 weeks prior to Cycle 1 Day 1

    Participants who have received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed
21. Last dose with any cytostatic treatments < 28 days before study treatment administration
22. Radiotherapy within the last 4 weeks before start of study treatment administration, with the exception of limited field palliative radiotherapy.
23. Administration of a live, attenuated vaccine within 4 weeks before Cycle 1 Day 1.
26. Severe dyspnea at rest or requiring supplementary oxygen therapy

Eligibility of participants who require blood transfusion before and after the start of the study treatment should be discussed by the Sponsor and Investigator.

Specific Exclusion Criteria for Participants in Part I:

27. Participants with pleural effusion (unilateral or bilateral) confirmed at screening by x-ray

Cohorts A and C: Checkpoint Inhibitor Naïve NSCLC Participants:

28. Previous CPI therapy (e.g., anti-CTLA-4, anti-PD-1/L1) before study enrollment

Cohort B: Checkpoint Inhibitor Experienced NSCLC Participants:

29. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
30. Any history of an immune-related Grade ≥3 adverse event (AE) attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

Cohort D: Checkpoint Inhibitor Experienced NSCLC Participants:

31. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
32. Any history of an immune-related Grade ≥ 3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)
33. Known sensitivity and contraindications to the comparative chemotherapy agent gemcitabine or vinorelbine

Cohort F: Checkpoint Inhibitor Experienced, Platinum Experienced, Docetaxel Naïve NSCLC Participants:

34. Participants treated with other non-platinum based chemotherapy treatment
35. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
36. Any history of an immune-related Grade ≥ 3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

Specific Exclusion Criteria for Participants in Part II:

37. Participants with pleural effusion (unilateral or bilateral) confirmed at screening by x-ray

Specific Exclusion Criteria for Participants in Part III:

38. Locally curative options are available for participant's disease

Cohorts G, I, J, K, M, & N: CPI-Naïve SCC Participants

39. Participants must not have received CPI therapy (e.g., anti CTLA-4, anti PD-1/L1) before study enrollment

Cohorts H & L: CPI-Experienced SCCHN Participants

40. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
41. Any history of an immune-related Grade ≥ 3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

NUMBER OF PARTICIPANTS

In Part I, Cohorts A, B, C, D, and F, which focuses on participants with advanced and/or metastatic NSCLC, approximately 110 response-evaluable participants will be enrolled (i.e., Cohorts A, B, and C with 20 participants each). In Cohort D, 120 participants were to be randomized to each schedule of the combination or to the control arm; however, the cohort is now closed with an enrollment of 10 participants. Cohort F will include 40 response-evaluable participants.

In Part II, Cohort E, which focuses on participants with previously untreated advanced and/or metastatic NSCLC, 80 response-evaluable participants will be randomized, with 40 participants in each schedule of the combination. The cohort is now closed with an enrollment of up to 10 participants.

In Part III, Cohorts G, H, I, J, K, L, M, and N, which focuses on participants with locally advanced or persistent or relapsed/recurrent and/or metastatic squamous cell carcinoma (SCC) will enroll 20 participants each. In any of these cohorts, the sample size may be extended to a total of 80 participants per cohort.

Other parts, focusing on other tumor types may be opened on the basis of emerging data from this study and other studies.

CONCOMITANT MEDICATIONS

Any medication or vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 30 days before screening until the *last* follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

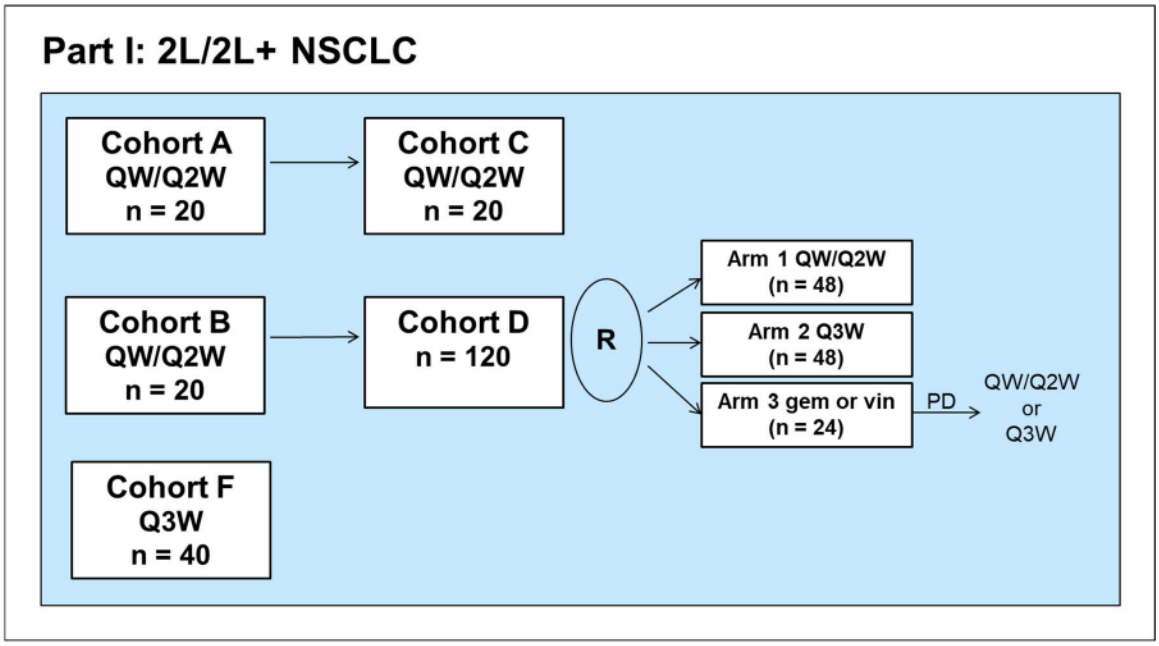
The Medical Monitor should be contacted if there are any questions regarding concomitant or previous therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic case report form.

1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1, Figure 2, and Figure 3.

Figure 1 Overview of Study Design – Part I (2L/2L+ NSCLC)



CPI = checkpoint inhibitor; FAP = fibroblast activation protein-α; gem = gemcitabine; NSCLC = non-small cell lung cancer; PD = progressive disease; QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks; R = randomization; vin = vinorelbine.

QW/Q2W schedule = *simlukafusp alfa* QW + atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* + atezolizumab Q2W.

Q3W schedule = *simlukafusp alfa* Q3W + atezolizumab Q3W.

Participant Characteristics for Part 1 = NSCLC Stage IV participants who have failed ≥ 1 line of therapy for metastatic disease, all PD-L1 expression levels, all FAP expression levels.

Cohorts A + C: CPI-naïve participants; QW/Q2W schedule.

Cohort B: CPI-experienced participants; QW/Q2W schedule.

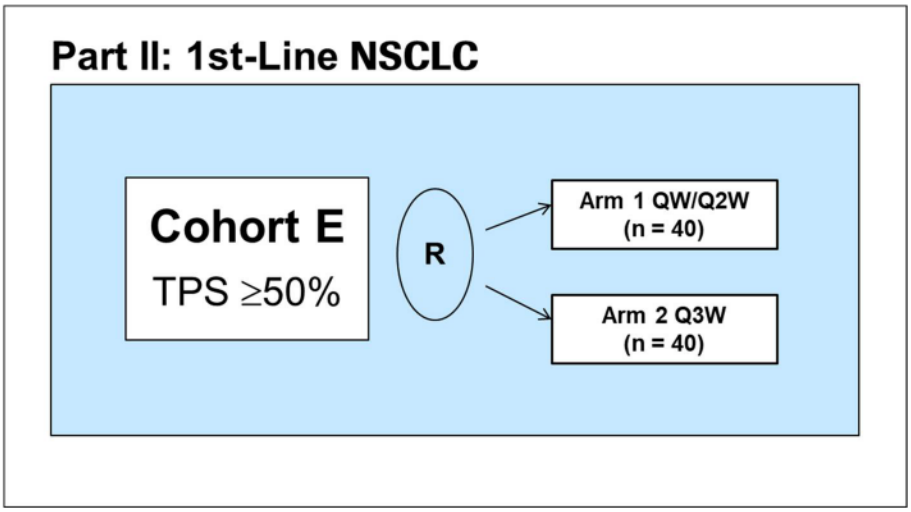
Cohort D: CPI-experienced participants; platinum pre-treated and docetaxel pre-treated.

- **Arm 1:** QW/Q2W schedule.
- **Arm 2:** Q3W schedule.
- **Arm 3:** Single-agent gemcitabine or vinorelbine.

Cohort F: CPI-experienced participants; platinum pre-treated; Q3W schedule.

Note: Recruitment into Cohort D has been closed early due to a change in the clinical development strategy.

Figure 2 Overview of Study Design – Part II



FAP = fibroblast activation protein-α; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; R = randomization; TPS = tumor proportion score; QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks.

QW/Q2W schedule = *simlukafusp alfa* QW + atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* + atezolizumab Q2W.

Q3W schedule = *simlukafusp alfa* Q3W + atezolizumab Q3W.

Participant Characteristics for Part II: NSCLC stage IV without prior treatment for metastatic disease (treatment naïve), high PD-L1 expression levels (TPS ≥ 50%, used interchangeably with tumor cell staining) all FAP expression levels.

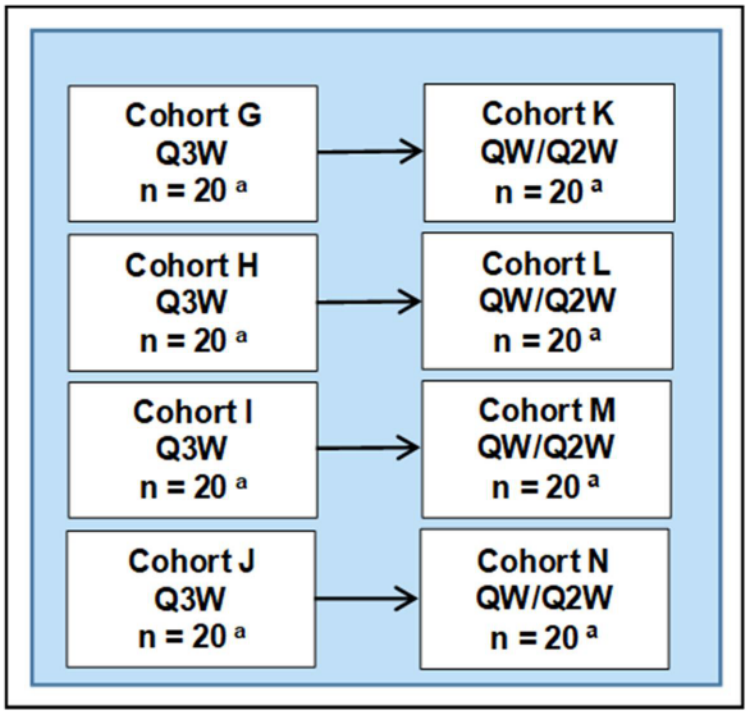
Cohort E:

Arm 1: QW/Q2W schedule.

Arm 2: Q3W schedule.

Note: Recruitment into Cohort E has been closed early due to a change in the clinical development strategy.

Figure 3 Overview of Study Design – Part III



CPI = checkpoint inhibitor; PD-L1 = programmed death-ligand 1; sq = squamous; SCCHN = squamous cell carcinoma of the head and neck; Q3W = every 3 weeks.

[a] n = 20, but can be expanded up to 80; applies to all cohorts.

Q3W schedule = *simlukafusp alfa* Q3W + atezolizumab Q3W.

QW/Q2W schedule = *simlukafusp alfa* QW + atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* + atezolizumab Q2W.

Participant Characteristics for Part III = participants with advanced and/or metastatic squamous cell carcinoma, irrespective of PD-L1 expression, will be divided into the following cohorts:

Cohort G: CPI-naïve SCCHN participants; Q3W schedule, 1L/1L+.
Cohort H: CPI-experienced SCCHN participants; Q3W schedule, 2L/2L+.
Cohort I: Esophageal squamous cell carcinoma participants; Q3W schedule, 2L/2L+.
Cohort J: Cervical squamous cell carcinoma participants; Q3W schedule, 2L/2L+.
Cohort K: CPI-naïve SCCHN participants; QW/Q2W schedule, 1L/1L+.
Cohort L: CPI-experienced SCCHN participants; QW/Q2W schedule, 2L/2L+.
Cohort M: Esophageal squamous cell carcinoma participants; QW/Q2W schedule, 2L/2L+.
Cohort N: Cervical SCC participants; QW/Q2W schedule, 2L/2L+.

Note: Additional parts (e.g., Part IV, Part V) may be opened at a later time investigating *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in other tumor types selected on the basis of emerging data from this study or information deriving from other studies (via an amendment).

1.3 SCHEDULE OF ACTIVITIES

The schedules of activities (SoA) are provided in Table 1 through Table 7. The SoA for infusion-related reactions (IRRs) and other unscheduled visits is provided in Table 8.

Table 1 Schedule of Activities – Parts I, II, and III Q2W Scheme (Cycles 1 – 3)

Cycle (14 days)	Screening/ Baseline	Cycle 1								Cycle 2						Cycle 3			
Day	-28 to -2	1	2	3	5	8	9	10	12	1	2	3	8	9	10	1	2	3	8
Time Relative (h)	***	0	24	48	96	168	192	216	264	0	24	48	168	192	216	0	24	48	168
Informed Consent [a]	x																		
Demography	x																		
Medical History	x																		
EBV and High-Risk HPV Status [b]	x																		
Physical Examination [c]	x	x				x				x			x			x			
Weight [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status/ KPS [d]	x	x				x				x			x			x			
Vital Signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Spirometry [f]	x																		
12-lead ECG [g]	x	x														x			
Hematology [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lipid Panel [h]	x																		
Blood Chemistry [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation [h, i]	x	x	x			x	x			x			x			x			x
Viral serology [j]	x																		
Urinalysis [h]	x	x				x				x			x			x			x
Pregnancy Test [k]	x															x			
Echocardiography (TTE/MUGA)	x																		
Administration of *simlukafusp alfa* [l]		x				x				x			x			x			
Administration of Atezolizumab		x								x						x			
PK *simlukafusp alfa* [m]		x	x			x				x	x	x							
ADA *simlukafusp alfa*		x				x				x									
PK Atezolizumab [m]		x	x			x				x									
ADA Atezolizumab		x								x									
PD Sample (FACS) Basic [n,o,p,q]		x				x				x			x			x			x
PD Sample (FACS) Advanced [n,o,p,q]		x								x						x			x
PD Sample (Plasma) [n,o,p,q]		x[r]	x			x				x	x		x			x			x
PD Sample (Serum) [n,q]		x[r]	x			x				x			x			x			x
Clinical Genotyping [s]	x																		
Archival Tumor Tissue [t]	x																		
Tumor Biopsy [p,t, bb]	x																		x[t]
Tumor Mutation Burden (Plasma) [u]		x																	
Tumor Assessment [v]	x																		
Pre-Study CT scan [w]	x																		
Chest X-ray [x]	x																		

Table 1 Schedule of Activities – Parts I, II, and III Q2W Scheme (Cycles 1 – 3) (Cont.)

Cycle (14 days)	Screening/ Baseline	Cycle 1								Cycle 2						Cycle 3			
Day	-28 to -2	1	2	3	5	8	9	10	12	1	2	3	8	9	10	1	2	3	8
Time Relative (h)	***	0	24	48	96	168	192	216	264	0	24	48	168	192	216	0	24	48	168
Serum TSH[y]	x																		
Auto-ant body Panel[z]	x																		
Adverse Events[aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous & Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CT = computed tomography scan; DNA = deoxyribonucleic acid; EBV = Epstein Barr virus; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FACS = fluorescence-activated cell sorting; FEV = forced expiratory volume; FVC = forced vital capacity; h = hour; HPV = human papilloma virus; INR = international normalized ratio; IRR = infusion/injection-related reaction; KPS = Karnofsky Performance Score; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; NK = natural killer; PD = pharmacodynamics; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; Q2W = every 2 weeks; SAE = serious adverse event; T_{reg} = regulatory T cell; TGK = tumor growth kinetic; TPS = tumor proportion score; TSH = thyroid stimulating hormone; TTE = transthoracic echocardiogram.

[a] Informed consent must be obtained before any study-specific procedures are conducted. The screening window clock starts with the first study-specific screening test or evaluation and not the consent date.

[b] Part III only: Information on the participant's EBV status and High risk/HR HPV status in tumor tissue should be recorded, as available, in the participant's file. Local results, if available, should be reported within 6 months of enrollment.

[c] Physical examinations will be done at screening and prior to study treatment administration on infusion days. Weight should be recorded prior to study treatment administration on infusion days. The site should instruct the participant to notify them in case weight gain is noticed (i.e., > 5% of weight gain).The participants should monitor their own weight at home (e.g., 3 times per week). Height is to be measured at screening only.

[d] ECOG Performance Status/KPS will be done at screening, prior to each study treatment administration, and as specified in this table. On dosing days, results may be obtained up to 72 hours prior to study treatment administration.

[e] Vital signs include seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature. Vital signs must be obtained at the timepoints specified in this table and in Table 3. During infusions, vital signs are not required to be captured in the eCRF, unless abnormalities are observed. Participants experiencing Grade ≥ 3 vital sign abnormalities at a previous cycle should stay at the site after the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[f] Spirometry (FEV and FVC) will be performed at screening and as clinically indicated. Participants experiencing Grade ≥ 3 FEV decrease at a previous cycle should stay at site at the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[g] Single 12-lead ECG recordings (i.e., qualitatively acceptable ECGs without artifacts) must be obtained at the timepoints specified in this table and in Table 3. ECGs should be performed before any scheduled vital sign measurements and blood draws.

Table 1 Schedule of Activities – Parts I, II, and III Q2W Scheme (Cycles 1 – 3) (Cont.)

[h] Hematology, blood chemistry, and coagulation panels and urinalysis can be performed up to 72 hours before a scheduled dosing as results must be available before dosing. Additional blood samples for hematology, blood chemistry, and coagulation parameters will be taken as specified in Table 3 and at the time of an IRR or hypersensitivity reaction. A lipid panel is to be obtained at screening and then every 8 weeks. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. As part of blood chemistry, troponin I or T measurement will be performed on D1 pre-dose of Cycle 1, 3, 5, 7, 9, and 11, and on discontinuation visit or 28-day follow-up visit and as clinically indicated.

[i] For coagulation parameters (including PT, INR, and PTT), an additional sample will be taken at the time of an IRR or hypersensitivity reaction, and as clinically indicated. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, PT, fibrin degradation products, D-dimer) may be assessed according to clinical judgment.

[j] A sample will be taken for serology for HIV and hepatitis A, B, C and E at screening and as clinically indicated in case of suspicion of a viral infection. Exclusion of patients with active hepatitis B is considered sufficient to exclude all patients with a potential active hepatitis D virus infection.

[k] A serum pregnancy test will be performed at screening (i.e., within 7 days before the first study treatment administration on Cycle 1 Day 1) and at the Day 28 follow-up visit and 120 days after the last dose of atezolizumab follow-up visit. In addition, a urine pregnancy test should be done every 4 weeks from Cycle 3 Day 1 (i.e., urine pregnancy test will be performed on Day 1 of Cycles 3, 5, 7, 9, etc.), discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[l] Administration of *simlukafusp alfa*: If the dose of *simlukafusp alfa* is intra-participant up-titrated, this should occur on Cycle 1 Day 8 and this dosage should be maintained as long as it is tolerated by the participant.

[m] PK samples for *simlukafusp alfa* and atezolizumab: See the hourly table for detailed collection times for the days indicated in this table and the subsequent cycles in which PK samples are to be collected.

[n] Blood samples for biomarker assessment have to be taken before study treatment administration on Cycle 1 Day1. "FACS Basic" includes analysis of T, B, and NK cell numbers; and "FACS Advanced" includes analysis of T_{reg} as well as T-cell proliferation and differentiation.

[o] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of a Grade ≥ 3 IRR.

[p] Optional biopsy of progressing and/or regressing lesions is desirable at the investigator's discretion, to characterize the participant's response to treatment. If the participant progresses and discontinues treatment before 4 weeks of treatment, the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced, and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[q] On Cycle 3 Day 8 (+2/-1 day[s]), PD samples need to be taken prior to the fresh biopsy, on the same day.

[r] Part III only: On Cycle 1 Day 1, an additional PD plasma and PD serum sample will be collected to allow for central laboratory virus testing (EBV, HPV).

[s] Clinical genotyping: A mandatory whole blood sample for DNA analysis will be taken any time after eligibility has been confirmed. If this sample is missed, it can be collected at any other scheduled visit but not later than 3 months after enrollment.

[t] Tumor biopsies: A mandatory archival tumor tissue sample is to be obtained within 2 months after enrollment. Fresh tumor biopsies, one *mandatory* at baseline (once eligibility has been confirmed, exception Cohorts E as stated below) and one *optional* on-treatment on Cycle 3 Day 8 (+2/-1 day[s]), will be collected. In Cohort A, the biopsies are optional. For Cohort E only, PD-L1 high status (Cohort E: TPS $\geq$ 50%) is required to confirm eligibility; therefore, an archival specimen containing adequate viable tumor tissue to establish PD-L1 expression status is required. If archival tissue (cohort E) is not available, PD-L1 will be performed on a fresh tumor biopsy which will also be used as the baseline biopsy if the participant is enrolled (i.e., a repeat biopsy is not necessary). Study Part III Cohorts G, H, K, and L only: For participants presenting with a single target lesion, which also is the only biopsiable one, no biopsies should be performed. For all cohorts, additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected in any participant, at the Investigator's discretion, to characterize the participant's response to treatment.

[u] Tumor Mutation Burden (Plasma): Samples to be taken before study drug administration

Table 1 Schedule of Activities – Parts I, II, and III Q2W Scheme (Cycles 1 – 3) (Cont.)

[v] Tumor assessment will be assessed at screening and every 8 weeks (±7 days) after study treatment for the first year. After the first year, in all cohorts except Cohort D, tumor assessments should be assessed every 12 weeks (±7 days); in Cohort D, tumor assessments should continue every 8 weeks (±7 days). Assessments continue until disease progression or study treatment discontinuation, whichever occurs last.

[w] Optional latest pre-study CT/MRI scans should be provided for assessment of TGK (within 12 weeks of Cycle 1 Day 1).

[x] Chest x-ray will be performed at screening (to obtain the baseline) and as clinically indicated during the study treatment period.

[y] Serum TSH level will be assessed at screening and on study (every 8 weeks from Cycle 1, Day 1). In case of abnormalities, the participant should be monitored until full resolution and a further analysis (i.e., free T3 and T4 serum level) is performed. An endocrinologist should be consulted if an endocrinopathy is suspected.

[z] The autoantibody panel will be assessed at screening and as clinically indicated. In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment, the auto-antibody panel should be repeated. Participants with confirmed positive serology of at least one of the parameters in the autoantibody panel during the course of the study should be discussed between Sponsor and Investigators and, if judged clinically relevant, could be referred to a specialist to exclude an underlying autoimmune disease.

[aa] SAEs occurring after signature of informed consent but before the first infusion of study treatment are reportable according to local regulations. SAEs related to study procedures are reportable after signature of informed consent. For SAEs before first dose, the corresponding AE page should also be completed.

[bb] In case *simlukafusp alfa* administration is omitted on Cycle 3 Day 1, the *optional* on-treatment tumor biopsy will be collected 7 days (+2/-1 day[s]) after the participant receives the next *simlukafusp alfa* dose administration in the upcoming cycle using an unscheduled kit. In such a case, PD samples (PD FACS Basic, PD FACS Advanced and PD Plasma) also will be collected on the day of the tumor biopsy using an unscheduled kit, while PD Serum is not collected (as not part of unscheduled kit).

Table 2 Schedule of Activities – Parts I, II, and III Q2W Scheme (Cycles 4+)

Cycle (14 days)	Cycle 4				Cycle 5		Cycle 6		Cycle 7	Cycle 8	Subsequent Cycles		Discon.	28-day Follow-up Visit (±3)	3-month Safety Follow-up (±7 days)	120 (±30) Days after Last Dose of A
Day	1 (±3)	2	3	8	1 (±3)	2	1 (±3)	2	1 (±3)	1 (±3)	1 (±3)	2				
Time Relative (h)	0	24	48	168	0	24	0	24	0	0	0	24	***	***	***	***
Physical Examination [a]	x				x		x		x	x	x		x	x	x	x
Weight [a]	x	x	x	x	x		x		x	x	x		x	x	x	x
ECOG Performance Status/ KPS [b]	x				x		x		x	x	x		x	x	x	x
Vital Signs [c]	x	x	x	x	x		x		x	x	x		x	x	x	x
Spirometry [d]																
12-lead ECG [e]													x	x		
Hematology [f]	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x
Lipid Panel [f]					x						x		x	x	x	x
Blood Chemistry [f]	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x
Coagulation [f,g]	x			x	x		x		x	x	x		x	x	x	x
Urinalysis [f]	x			x	x		x		x	x	x		x	x	x	
Pregnancy Test [h]					x				x		x		x	x		x
Echocardiography (TTE/MUGA)													x			
Administration of *simlukafusp alfa* [i]	x				x		x		x	x	x					
Administration of Atezolizumab	x				x		x		x	x	x					
PK *simlukafusp alfa* [j]	x	x	x							x	x [j]	x [j]	x			x
ADA *simlukafusp alfa*	x									x	x		x			x
PK Atezolizumab [j]	x									x	x [j]		x			x
ADA Atezolizumab	x									x	x		x			x
PD Sample (FACS) Basic [k,l,m,n]	x			x			x				x [m,o]			x	x	x
PD Sample (FACS) Advanced [k,l,m,n]							x				x [m,o]					
PD Sample (Plasma) [k,l,m,n]	x	x					x				x [m,o]			x	x	x
PD Sample (Serum) [k,n]	x						x				x [m,o]			x		
Tumor Biopsy [m,o]											x [m, o]					
Tumor Assessment [p]					x [p]						x [p]					
Serum Thyroid-Stimulating Hormone [q]					x						x [q]		x	x	x	x
Auto-antibody Panel [r]																
Survival Follow-Up [s]																x
Post-study anti-cancer therapies [s]													x		x	

Table 2 Schedule of Activities Parts I, II, and III Q2W Scheme (Cycles 4+) (Cont.)

Cycle (14 days)	Cycle 4				Cycle 5		Cycle 6		Cycle 7	Cycle 8	Subsequent Cycles		Discon.	28-day Follow-up Visit (±3)	3-month Safety Follow-up (±7 days)	120 (±30) Days after Last Dose of A
Day	1 (±3)	2	3	8	1 (±3)	2	1 (±3)	2	1 (±3)	1 (±3)	1 (±3)	2				
Time Relative (h)	0	24	48	168	0	24	0	24	0	0	0	24	***	***	***	***
Adverse Events [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous & Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: A = atezolizumab; AE = adverse event; Discon. = Discontinuation Visit; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FACS = fluorescence-activated cell sorting; FEV = forced expiratory volume; FVC = forced vital capacity; h = hour; INR = international normalized ratio; IRR = infusion/injection-related reaction; KPS = Karnofsky Performance Score; MUGA = multigated acquisition scan; NK = natural killer; PD = pharmacodynamics; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; T_{reg} = regulatory T cells; TGK = tumor growth kinetic; TPS = tumor proportion score; TSH = thyroid stimulating hormone; TTE = transthoracic echocardiogram.

[a] Physical Examinations will be done at screening and prior to study treatment administration on infusion days. Weight should be recorded prior to study treatment administration on infusion days. The site should instruct the participant to notify them in case weight gain is noticed (i.e., > 5% of weight gain).The participants should monitor their own weight at home (e.g., 3 times per week). Height is to be measured at screening only.

[b] ECOG Performance Status/KPS will be done at screening, prior to each study treatment administration, and as specified in this table. On dosing days, results may be obtained up to 72 hours prior to study treatment administration.

[c] Vital signs include seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature. Vital signs must be obtained at the timepoints specified in this table and in Table 3. During infusions, vital signs are not required to be captured in the eCRF, unless abnormalities are observed. Participants experiencing Grade ≥ 3 vital sign abnormalities at a previous cycle should stay at the site after the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[d] Spirometry (forced expiratory volume [FEV] and forced vital capacity [FVC]) will be performed at screening and as clinically indicated. Participants experiencing Grade ≥ 3 FEV decrease at a previous cycle should stay at site at the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[e] Single 12-lead ECG recordings (i.e., qualitatively acceptable ECGs without artifacts) must be obtained at the timepoints specified in this table and in Table 3. ECGs should be performed before any scheduled vital sign measurements and blood draws.

[f] Hematology, blood chemistry, and coagulation panels and urinalysis can be performed up to 72 hours before a scheduled dosing as results must be available before dosing. Additional blood samples for hematology, blood chemistry, and coagulation parameters will be taken as specified in Table 3 and at the time of an IRR or hypersensitivity reaction. A lipid panel is to be obtained at screening and then every 8 weeks. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. As part of blood chemistry, troponin I or T measurement will be performed on D1 pre-dose of Cycle 1, 3, 5, 7, 9, and 11, and on discontinuation visit or 28-day follow-up visit and as clinically indicated.

[g] For coagulation parameters (including PT, INR, and PTT), an additional sample will be taken at the time of an IRR or hypersensitivity reaction, and as clinically indicated. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, PT, fibrin degradation products, D-dimer) may be assessed according to clinical judgment.

[h] A serum pregnancy test will be performed at screening (i.e., within 7 days before the first study treatment administration on Cycle 1 Day 1) and at the Day 28 follow-up visit and 120 days after the last dose of atezolizumab follow-up visit. In addition, a urine pregnancy test should be done every 4 weeks from Cycle 3

Table 2 Schedule of Activities Parts I, II, and III Q2W Scheme (Cycles 4+) (Cont.)

Day 1 (i.e., urine pregnancy test will be performed on Day 1 of Cycles 3, 5, 7, 9, etc.), discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[i] Administration of *simlukafusp alfa*: if the dose of *simlukafusp alfa* is intra-participant up-titrated, this should occur on Cycle 1 Day 8 and this dosage should be maintained as long as it is tolerated by the participant.

[j] PK samples for *simlukafusp alfa* and atezolizumab: See the hourly table for detailed collection times for the days indicated in this table and the subsequent cycles in which PK samples are to be collected.

[k] Blood samples for biomarker assessment have to be taken before study treatment administration on Cycle 1 Day1. "FACS Basic" includes analysis of T, B, and NK cell numbers; and "FACS Advanced" includes analysis of T_{reg} as well as T-cell proliferation and differentiation.

[l] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of a Grade ≥ 3 IRR.

[m] Optional biopsy of progressing and/or regressing lesions is desirable at the investigator's discretion, to characterize the participant's response to treatment. If the participant progresses and discontinues treatment before the scheduled biopsy timepoint, the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced, and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[n] On Cycle 3 Day 8 (+2/-1 day[s]), PD samples need to be taken prior to the fresh biopsy, on the same day.

[o] Tumor biopsies: A mandatory archival tumor tissue sample is to be obtained within 2 months after enrollment. Fresh tumor biopsies, one *mandatory* at baseline (once eligibility has been confirmed, exception Cohort E as stated below) and one *optional* on-treatment at Cycle 3 Day 8 (+2/-1 day[s]), will be collected. In Cohort A, the biopsies are optional. For Cohort E only, PD-L1 high status (i.e., TPS $\geq 50\%$) is required to confirm eligibility; therefore, an archival specimen containing adequate viable tumor tissue to establish PD-L1 expression status is required. If archival tissue is not available, PD-L1 will be performed on a fresh tumor biopsy which will also be used as the baseline biopsy if the participant is enrolled (i.e., a repeat biopsy is not necessary). Study Part III Cohorts G, H, K and L only: For participants presenting with a single target lesion, which also is the only biopsiable one, no biopsies should be performed. For all cohorts, additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected in any participant, at the Investigator's discretion, to characterize the participant's response to treatment.

[p] Tumor assessment will be assessed at screening and every 8 weeks (± 7 days) after study treatment for the first year. After the first year, in all cohorts except Cohort D, tumor assessments should be assessed every 12 weeks (± 7 days); in Cohort D, tumor assessments should continue every 8 weeks (± 7 days). Assessments continue until disease progression or study treatment discontinuation, whichever occurs last.

[q] Serum TSH level will be assessed at screening and on study (every 8 weeks from Cycle 1, Day 1). In case of abnormalities, the participant should be monitored until full resolution and a further analysis (i.e., free T3 and T4 serum level) is performed. An endocrinologist should be consulted if an endocrinopathy is suspected.

[r] The autoantibody panel will be assessed at screening and as clinically indicated. In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment, the auto-antibody panel should be repeated. Participants with confirmed positive serology of at least one of the parameters in the autoantibody panel during the course of the study should be discussed between Sponsor and Investigators and, if judged clinically relevant, could be referred to a specialist to exclude an underlying autoimmune disease.

[s] Survival Follow-Up: Every 3 months ($\pm$ 30 days), starting at Day 120 visit ($\pm$30 days), the sites will provide the Sponsor an update on the survival status of each participant enrolled in the study. Post-study anti-cancer therapies should be collected and reported as appropriate in the eCRF.

[t] SAEs occurring after signature of informed consent but before the first infusion of study treatment are reportable according to local regulations. SAEs related to study procedures are reportable after signature of informed consent. For SAEs before first dose, the corresponding AE page should also be completed.

Table 3 Schedule of Activities – Parts I, II, and III Q2W Scheme (Hourly)

Cycle	Day	Scheduled Time (h)	Time Window	Vital Signs [a]	12-lead ECG [b]	Routine Laboratory [c]			*Simlukafusp alfa*		Atezolizumab		PD Sample (FACS)		PD Sample		Tumor Biopsy
						Hema	Chem	Coag	PK [d]	ADA [e]	PK	ADA	Basic [f]	Adv [f]	Plasma [f]	Serum	
1	1	Predose A	-4h	x	x	x [c]	x [c]	x [c]			x	x	x	x	x [g]	x [g]	
		EOI+0.5 A	±5min								x						
		Predose F	-4h	x					x	x							
		EOI F	±15min	x	x				x								
		EOI+2 F	±30min	x													
		EOI+6 F	±30min	x													
		EOI+8 F	±30min	x													
	2	24 A	±2h								x						
		24 F	±2h	x		x	x	x	x						x	x	
	3 [h]	48 F	-2h/+48h	x		x	x										
	5 [h]	96 F	-2h/+48h	x		x	x										
	8	Predose F	-4h	x		x [c]	x [c]	x [c]	x	x	x		x		x	x	
		EOI F	±15min	x					x								
		EOI+2 F	±1h	x		x	x										
		EOI+6 F	±1h	x													
	9	24 F	±2h	x		x	x	x									
	10 [h]	48 F	-2h/+48h	x		x	x										
	12 [h]	96 F	-2h/+48h	x		x	x										
2	1	Predose A	-4h	x		x [c]	x [c]	x [c]			x	x	x	x	x	x	
		Predose F	-4h	x					x	x							
		EOI F	±15min	x					x								
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x		x						x		
	3	48 F	-2h/+48h	x		x	x		x								
	8	Predose F	-4h	x		x [c]	x [c]	x [c]					x		x	x	
		EOI F	±15min	x		x	x										
	9	24 F	±2h	x		x	x										
	10	48 F	-2h/+48h	x		x	x										
3	1	Predose A	-4h	x	x	x [c]	x [c]	x [c]					x	x	x	x	
		Predose F	-4h	x													

Table 3 Schedule of Activities – Parts I, II, and III Q2W Scheme (Hourly) (Cont.)

Cycle	Day	Scheduled Time (h)	Time Window	Vital Signs [a]	12-lead ECG [b]	Routine Laboratory [c]			*Simlukafusp alfa*		Atezolizumab		PD Sample (FACS)		PD Sample		Tumor Biopsy
						Hema	Chem	Coag	PK [d]	ADA [e]	PK	ADA	Basic [f]	Adv [f]	Plasma [f]	Serum	
		EOI F	±15min	x	x												
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x										
	3	48 F	-2h/+48h	x		x	x										
	8	168 F	-2h/+48h	x		x	x	x					x [i]	x [i]	x [i]	x [i]	x [i, j, m]
4	1 (±3)	Predose A	-4h			x [c]	x [c]	x [c]			x	x	x		x	x	
		Predose F	-4h	x					x	x							
		EOI F	±15min	x					x								
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x		x						x		
	3	48 F	-2h/+48h	x		x	x		x								
	8	168 F	-2h/+48h	x		x	x	x					x				
5	1 (±3)	Predose	-4h	x		x [c]	x [c]	x [c]									
		EOI F	±15min	x													
		EOI+2F	±1h	x													
	2	24 F	±2h			x	x										
6	1 (±3)	Predose	-4h	x		x [c]	x [c]	x [c]					x	x	x	x	
		EOI F	±15min	x													
		EOI+2F	±1h	x													
	2	24 F	±2h			x	x										
7	1 (±3)	Predose	-4h	x		x [c]	x [c]	x [c]									
		EOI+2F	±1h	x													
8	1 (±3)	Predose	-4h	x		x [c]	x [c]	x [c]	x [e, j]	x [e]	x [k]	x [k]					
		EOI+2F	±1h	x					x								
Subsequent Cycles		At visit		x		x [c]	x [c]	x [c]					x [i]	x [i]	x [i]	x [i]	x [i, j]
Every TA	1 (±3)	Predose	-4h						x [e, j]	x [e]	x [k]	x [k]					
		EOI F	±15min						x [l]								
	2	24 F	±4h						x [l]								
Discontinuation		At visit		x	x	x	x	x	x	x	x	x					
28-Day		At visit		x	x	x	x	x					x		x	x	

Table 3 Schedule of Activities – Parts I, II, and III Q2W Scheme (Hourly) (Cont.)

Cycle	Day	Scheduled Time (h)	Time Window	Vital Signs [a]	12-lead ECG [b]	Routine Laboratory [c]			*Simlukafusp alfa*		Atezolizumab		PD Sample (FACS)		PD Sample		Tumor Biopsy
						Hema	Chem	Coag	PK [d]	ADA [e]	PK	ADA	Basic [f]	Adv [f]	Plasma [f]	Serum	
F/U Visit																	
3-month Safety F/U		At visit		x		x	x	x					x		x		
120 (±30) days after last dose of atezolizumab		At visit		x		x	x	x		x		x	x		x		

Abbreviations: A = atezolizumab; ADA = anti-drug antibody; AE = adverse event; C = cycle; Chem = blood chemistry; Coag = coagulation; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; F = FAP-IL2v (*simlukafusp alfa*); FACS = fluorescence-activated cell sorting; F/U = follow-up; h = hour; Hema = hematology; IgE = immunoglobulin E; IRR = infusion/injection-related reaction; min = minutes; PD = pharmacodynamics; PK = pharmacokinetic; TMB = tumor mutation burden; TA = tumor assessment.

[a] Vital signs (including sitting or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature; with pulse oximetry at the times indicated in this table, as per Table 11 for *simlukafusp alfa* and as per Table 12 for atezolizumab. Vital signs should be measured within 60 minutes prior to the atezolizumab infusion.

[b] Single 12-lead ECG will be obtained at screening, at pre-infusion, at the end of infusion on Cycle 1 Day 1 and Cycle 3 Day 1, at treatment discontinuation, and at the 28-day safety follow-up visit. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done before any vital sign measurement or blood collections.

[c] Hematology, blood chemistry, coagulation, and urinalysis can be performed up to 72 hours before scheduled dosing as results must be available before dosing. A lipid panel is to be obtained at screening and then every 8 weeks.

[d] Additional PK samples will be taken if a participant withdraws or has an IRR or an AE leading to dose reduction or delay of *simlukafusp alfa* administration. During the course of the study, PK/PD sampling timepoints may be modified based on emerging data to ensure that PK/PD of *simlukafusp alfa* can be adequately characterized. In this case, no new additional PK/PD samples will be introduced but sampling times may be modified or reduced.

[e] Blood for ADA *simlukafusp alfa* determination will be taken on Cycle 8 Day 1. Afterwards, samples will be taken on Day 1 in cycles when a tumor assessment is performed. Blood for ADA determination with a corresponding PK sample should always be taken pre-dose. Additional samples for ADA *simlukafusp alfa* and PD sample (Plasma) will be taken at the time of an IRR or of hypersensitivity reaction for analysis of IgE/tryptase and ADA (Table 8), at treatment discontinuation (ADA sample only) and 120 days follow-up.

[f] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of an Grade ≥ 3 IRR.

[g] Part III only: On Cycle 1 Day 1, an additional PD plasma and PD serum sample will be collected to allow for central laboratory virus testing (EBV, HPV).

[h] The time windows should be used for flexibility but the visits should not be merged. For example, if dosing occurs on a Thursday, to avoid a weekend visit, the Day 3 could be conducted on the following Monday and the Day 5 on the Wednesday.

[i] The on-treatment biopsy is to be collected at Cycle 3 Day 8 (+2/-1 day[s]). This biopsy is optional. Study Part III Cohorts G, H, K and L only: For participants presenting with a single target lesion, which also is the only biopsiable one, no biopsies should be performed. For all cohorts, optional biopsy of progressing and/or regressing lesions is desirable. If the participant progresses and discontinues treatment before the scheduled biopsy timepoint, the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[j] Flexibility of +2/-1 day[s] aligned with biopsy.

Table 3 Schedule of Activities – Parts I, II, and III Q2W Scheme (Hourly) (Cont.)

[k] PK atezolizumab and ADA atezolizumab samples will be taken on Cycle 8 Day 1 then every 8 cycles from this timepoint onwards.

[l] PK *simlukafusp alfa* samples will be taken on Cycle 8 Day 1 and then at Cycle 13 Day 1 and Day 2. Afterwards, samples will be taken on Day 1 in cycles when a tumor assessment is performed.

[m] In case *simlukafusp alfa* administration is omitted on Cycle 3 Day 1, the *optional* on-treatment tumor biopsy will be collected 7 days (+2/-1 day[s]) after the participant receives the next *simlukafusp alfa* dose administration in the upcoming cycle using an unscheduled kit. In such a case, PD samples (PD FACS Basic, PD FACS Advanced and PD Plasma) also will be collected on the day of the tumor biopsy using an unscheduled kit, while PD Serum is not collected (as not part of unscheduled kit).

Table 4 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 1 – 3)

Cycle (21 days)	Screening / Baseline	Cycle 1					Cycle 2				Cycle 3				
Day	-28 to -2	1	2	3	5	8	1 (±3)	2	3	8	1 (±3)	2	3	8	15
Time Relative (h)	***	0	24	48	96	168	0	24	48	168	0	24	48	168	336
Informed Consent [a]	x														
Demography	x														
Medical History	x														
EBV and High Risk HPV Status [b]	x														
Physical Examination [c]	x	x					x				x				
Weight [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status/ KPS [d]	x	x					x				x				
Vital Signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Spirometry [f]	x														
12-lead ECG [g]	x	x									x				
Hematology [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood Chemistry [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Lipid Panel [h]	x														
Coagulation [h,i]	x	x	x			x	x			x	x			x	
Viral serology [j]	x														
Urinalysis [h]	x	x				x	x			x	x			x	
Pregnancy Test [k]	x										x				
Echocardiography (TTE/MUGA)	x														
Administration of *simlukafusp alfa* [l]		x					x				x				
Administration of Atezolizumab		x					x				x				
PK *simlukafusp alfa*		x	x	x		x	x				x	x	x	x	
ADA *simlukafusp alfa*		x					x				x				
PK Atezolizumab		x				x	x				x				
ADA Atezolizumab		x					x				x				
PD Sample (FACS) Basic [m,n,o]		x				x	x			x [o]	x			x	
PD Sample (FACS) Advanced [m,n,o]		x				x	x			x [o]	x				
PD Sample (Plasma) [m,n,o]		x [p]	x			x	x	x		x [o]	x			x	
PD Sample (Serum) [n,o]		x [p]	x			x	x			x [o]	x			x	
Clinical Genotyping [q]	x														
Tumor Mutation Burden (Plasma)		x													
Archival Tumor Tissue [r]	x														
Tumor Biopsy [r, s, z]	x									x [r]					
Tumor Assessment [t]	x														x [r]

Table 4 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 1 – 3) (Cont.)

Cycle (21 days)	Screening / Baseline	Cycle 1					Cycle 2				Cycle 3				
Day	-28 to -2	1	2	3	5	8	1 (±3)	2	3	8	1 (±3)	2	3	8	15
Time Relative (h)	***	0	24	48	96	168	0	24	48	168	0	24	48	168	336
Pre-Study CT scan [u]	x														
Chest x-ray [v]	x														
Serum Thyroid-Stimulating Hormone [w]	x														
Auto-ant body Panel [x]	x														
Adverse Events [y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FACS = fluorescence-activated cell sorting; FEV = forced expiratory volume; FVC = forced vital capacity; h = hour; INR = international normalized ratio; IRR = infusion/injection-related reaction; KPS = Karnofsky Performance Score; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; NK = natural killer; PD = pharmacodynamics; PK = pharmacokinetic; PT = prothrombin time; PTT = partial prothrombin time; SAE = serious adverse event; TGK = tumor growth kinetic; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram.

[a] Informed consent must be obtained before any study-specific procedures are conducted. The screening window clock starts with the first study-specific screening test or evaluation and not the consent date.

[b] Part III only: Information on the participant's EBV status and High risk/HR HPV status in tumor tissue should be recorded, as available, in the participant's file. Results will not be utilized to determine participants' eligibility and should be reported within 6 months of enrollment.

[c] Physical Examination will be done at screening and prior to study treatment administration on infusion days. Weight should be recorded prior to study treatment administration on infusion days. The site should instruct the participant to notify them in case weight gain is noticed (i.e., > 5% of weight gain).The participants should self-monitor their bodyweight at home (e.g., 3 times per week). Height is to be measured at screening only.

[d] ECOG Performance Status/KPS will be done at screening, prior to each study treatment administration, and as specified in this table. On dosing days, results may be obtained up to 72 hours prior to study treatment administration.

[e] Vital signs include seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature. Vital signs must be obtained at the timepoints specified in this table and in Table 6. During infusions, vital signs are not required to be captured in the eCRF, unless abnormalities are observed. Participants experiencing Grade ≥ 3 vital sign abnormalities at a previous cycle should stay at the site after the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[f] Spirometry (FEV and FVC) will be performed at screening and as clinically indicated. Participants experiencing Grade ≥ 3 FEV decrease at a previous cycle should stay at site at the next study treatment administration for at least 24 hours post-infusions.

[g] Single 12-lead ECG recordings (i.e., qualitatively acceptable ECGs without artifacts) must be obtained at the timepoints specified in this table and in Table 6. ECGs should be performed before any scheduled vital sign measurements and blood draws.

Table 4 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 1 – 3) (Cont.)

[h] Hematology, blood chemistry, and coagulation panels and urinalysis can be performed up to 72 hours before a scheduled dosing as results must be available before dosing. Additional blood samples for hematology, blood chemistry, and coagulation parameters will be taken as specified in Table 6 and at the time of an IRR or hypersensitivity reaction. A lipid panel is to be obtained at screening and then every 9 weeks. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. As part of blood chemistry, troponin I or T measurement will be performed on D1 pre-dose of Cycle 1, 2, 3, 4, 6, 8, 10, and on discontinuation visit or 28-day follow-up visit and as clinically indicated.

[i] For coagulation parameters (including PT, INR, and PTT), an additional sample will be taken at the time of an IRR or hypersensitivity reaction, and as clinically indicated. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, PT, fibrin degradation products, D-dimer) may be assessed according to clinical judgment.

[j] A sample will be taken for serology for HIV, hepatitis A, B, C and E at screening and as clinically indicated in case of suspicion of a viral infection. Exclusion of patients with active hepatitis B is considered sufficient to exclude all patients with a potential active hepatitis D virus infection.

[k] A serum pregnancy test will be performed at screening (i.e., within 7 days before the first study treatment administration on Cycle 1 Day 1) and at the Day 28 Follow-up Visit and 120 Days after the Last Dose of Atezolizumab Follow-up Visit. In addition, a urine pregnancy test should be done every 6 weeks from Cycle 3 Day 1 (i.e., urine pregnancy test will be performed on Day 1 of Cycles 3, 5, 7, 9, etc.), discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[l] Administration of *simlukafusp alfa*: the dose of *simlukafusp alfa* will remain consistent as long as it is tolerated by the participant (i.e., there is no up-titration in the Q3W dosing schema).

[m] Blood samples for baseline biomarker assessments have to be taken before study treatment administration on Cycle 1 Day 1. "FACS Basic" includes analysis of T, B, and NK cell numbers; and "FACS Advanced" includes analysis of T_{reg} as well as T-cell proliferation and differentiation.

[n] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of a Grade $\geq$ 3 IRR.

[o] On Cycle 2 Day 8 (+2/-1 day[s]), PD samples need to be taken prior to the fresh biopsy, on the same day.

[p] Part III only: On Cycle 1 Day 1, an additional PD plasma and PD serum sample will be collected to allow for central laboratory virus testing (EBV, HPV).

[q] Clinical genotyping: A mandatory whole blood sample for DNA analysis will be taken any time after eligibility has been confirmed. If this sample is missed, it can be collected at any other scheduled visit but not later than 3 months after enrollment.

[r] Tumor biopsies: A mandatory archival tumor tissue sample is to be obtained from all participants within 2 months after enrollment. Two fresh tumor biopsies, one at baseline (once eligibility has been confirmed, exception Cohort E as stated below) and one on-treatment at Cycle 2 Day 8 (+2/-1 day[s]), will be collected. *The on-treatment biopsy is optional.* For Cohort E only, PD-L1 high status (i.e., TPS $\geq$ 50%) is required to confirm eligibility; therefore, an archival specimen containing adequate viable tumor tissue to establish PD-L1 expression status is required. If archival tissue is not available, PD-L1 will be performed on a fresh tumor biopsy which will also be used as the baseline Biopsy if the participant is enrolled (i.e., a repeat biopsy is not necessary). Study Part III Cohorts G, H, K and L only: For participants presenting with a single target lesion, which also is the only biopsiable one, no biopsies should be performed. For all cohorts, additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected in any participant, at the Investigator's discretion, to characterize the participant's response to treatment.

[s] Optional biopsy of progressing and/or regressing lesions is desirable at the investigator's discretion, to characterize the participant's response to treatment. If the participant progresses and discontinues treatment before the scheduled biopsy timepoint the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced, and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[t] Tumor assessment will be assessed at screening and every 8 weeks ($\pm$7 days) after study treatment for the first year. After the first year, all cohorts except Cohort D, tumor assessments should be assessed every 12 weeks ($\pm$7 days); in Cohort D, tumor assessments should continue every 8 weeks ($\pm$7 days). Assessments continue until disease progression or study treatment discontinuation, whichever occurs last.

[u] Optional latest pre-study CT/MRI scan should be provided for assessment of TGK (within 12 weeks of Cycle 1 Day 1).

Table 4 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 1 – 3) (Cont.)

[v] Chest x-ray will be performed at screening (to obtain the baseline) and as clinically indicated during the study treatment period.

[w] Serum TSH level will be assessed at screening and on study (every 9 weeks from Cycle 1, Day 1). In case of abnormalities, the participant should be monitored until full resolution and further analysis (i.e., T3 and T4 serum level) performed. An endocrinologist should be consulted if an endocrinopathy is suspected.

[x] The autoantibody panel will be assessed at screening and as clinically indicated. In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment, the auto-antibody panel should be repeated. Participants with confirmed positive serology of at least one of the parameters in the autoantibody panel during the course of the study should be discussed between Sponsor and Investigators and, if judged clinically relevant, could be referred to a specialist to exclude an underlying autoimmune disease.

[y] SAEs occurring after signature of informed consent but before the first infusion of study treatment are reportable according to local regulations. SAEs related to study procedures are reportable after signature of informed consent. For SAEs before first dose, the corresponding AE page should also be completed.

[z] In case *simlukafusp alfa* administration is omitted on Cycle 2 Day 1, the *optional* on-treatment tumor biopsy will be collected 7 days (+2/-1 day[s]) after the participant receives the next *simlukafusp alfa* dose administration in the upcoming cycle using an unscheduled kit. In such a case, PD samples (PD FACS Basic, PD FACS Advanced and PD Plasma) also will be collected on the day of the tumor biopsy using an unscheduled kit, while PD Serum is not collected (as not part of unscheduled kit).

Table 5 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 4+)

Cycle (21 days)	Cycle 4				Cycle 5		Cycle 6			Cycle 7	Cycle 8	Subsequent Cycles	Discon.	28-Day Follow-up Visit (±3)	3-month Safety Follow-Up (±7 days)	120 (±30) Days after Last Dose of A
Day	1 (±3)	2	3	8	1 (±3)	2	1 (±3)	2 [a]	8	1 (±3)	1 (±3)	1 (±3)				
Time Relative (h)	0	24	48	168	0	24	0	24	168	0	0	0	***	***	***	***
Physical Examination [b]	x				x		x			x	x	x	x	x	x	x
Weight [b]	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
ECOG Performance Status/ KPS [c]	x				x		x			x	x	x	x	x	x	x
Vital Signs [d]	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
12-lead ECG [e]													x	x		
Hematology [f]	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
Blood Chemistry [f]	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
Lipid Panel [f]	x									x		x [f]	x	x	x	x
Coagulation [f,g]	x			x	x		x			x	x	x	x	x	x	x
Viral serology [h]																
Urinalysis [f]	x			x	x		x			x	x	x	x	x	x	
Pregnancy Test [i]					x					x		x	x	x		x
Echocardiography (TTE/MUGA)													x			
Administration of *simlukafusp alfa* [j]	x				x		x			x	x	x				
Administration of Atezolizumab	x				x		x			x	x	x				
PK *simlukafusp alfa*	x				x							x	x	x	x	
ADA *simlukafusp alfa*	x				x							x	x	x	x	x
PK Atezolizumab	x				x							x	x	x		x
ADA Atezolizumab	x				x							x	x	x		x
PD Sample (FACS) Basic [k,l,m]	x			x			x					x [l, o]		x	x	x
PD Sample (FACS) Advanced [k,l,m]	x						x					x [l, o]				
PD Sample (Plasma) [k,l,m]	x	x					x					x [l, o]		x	x	x
PD Sample (Serum) [l,m]	x						x					x [l, o]		x		
Tumor Biopsy [n, o, u]												x [n,o]				
Tumor Assessment [p]									x [p]			x [p]				
Serum Thyroid-Stimulating Hormone [q]	x									x		x	x	x	x	x

Table 5 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 4+) (Cont.)

Cycle (21 days)	Cycle 4				Cycle 5		Cycle 6			Cycle 7	Cycle 8	Subsequent Cycles	Discon.	28-Day Follow-up Visit (±3)	3-month Safety Follow-Up (±7 days)	120 (±30) Days after Last Dose of A
Day	1 (±3)	2	3	8	1 (±3)	2	1 (±3)	2 [a]	8	1 (±3)	1 (±3)	1 (±3)				
Time Relative (h)	0	24	48	168	0	24	0	24	168	0	0	0	***	***	***	***
Autoantibody Panel [r]																
Survival Follow-Up [s]																x
Post-study anti-cancer therapies [s]													x		x	
Adverse Events [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous & Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: ADA = anti-drug antibody; AE = adverse event; c ANCA = circulating anti-neutrophil cytoplasmic antibody; COPD = chronic obstructive pulmonary disorder; CT = computed tomography;; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FACS = fluorescence-activated cell sorting; FAP = fibroblast activation protein-A; FEV = forced expiratory volume; F/U = follow-up; FVC = forced vital capacity; Ig = immunoglobulin; INR = international normalized ratio; IRR = infusion/injection-related reaction; KPS = Karnofsky Performance Score; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scans; NK = natural killer; p ANCA = perinuclear anti-neutrophil cytoplasmic antibody; PD = pharmacodynamics; PK = pharmacokinetic; PT = prothrombin time; PTT = partial prothrombin time; SAE = serious adverse event; TGK = tumor growth kinetic; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram.

[a] Starting at Cycle 6, the Day 2 visits might be omitted based on the emerging safety data.

[b] Physical Examination will be done at screening and prior to study treatment administration on infusion days. Weight should be recorded prior to study treatment administration on infusion days. The site should instruct the participant to notify them in case weight gain is noticed (i.e., > 5% of weight gain).The participants should monitor their own weight at home (e.g., 3 times per week). Height is to be measured at screening only.

[c] ECOG Performance Status/KPS will be done at screening, prior to each study treatment administration, and as specified in this table. On dosing days, results may be obtained up to 72 hours prior to study treatment administration.

[d] Vital signs include seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature. Vital signs must be obtained at the timepoints specified in this table and in Table 6. During infusions, vital signs are not required to be captured in the eCRF, unless abnormalities are observed. Participants experiencing Grade ≥ 3 vital sign abnormalities at a previous cycle should stay at the site after the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[e] Single 12-lead ECG recordings (i.e., qualitatively acceptable ECGs without artifacts) must be obtained at the timepoints specified in this table and in Table 6. ECGs should be performed before any scheduled vital sign measurements and blood draws.

[f] Hematology, blood chemistry, and coagulation panels and urinalysis can be performed up to 72 hours before a scheduled dosing as results must be available before dosing. Additional blood samples for hematology, blood chemistry, and coagulation parameters will be taken as specified in Table 6 and at the time of an IRR or hypersensitivity reaction. A lipid panel is to be obtained at screening and then every 9 weeks. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. As part of blood chemistry, troponin I or T measurement will be performed, on D1 pre-dose of cycle 1, 2, 3, 4, 6, 8, 10, and on discontinuation visit or 28-day follow-up visit and as clinically indicated.

Table 5 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 4+) (Cont.)

[g] For coagulation parameters (including PT, INR, and PTT), an additional sample will be taken at the time of an IRR or hypersensitivity reaction, and as clinically indicated. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, prothrombin time, fibrin degradation products, D-dimer) may be assessed according to clinical judgment.

[h] A sample will be taken for serology for HIV, hepatitis A, B, C and E at screening and as clinically indicated in case of suspicion of a viral infection. Exclusion of patients with active hepatitis B is considered sufficient to exclude all patients with a potential active hepatitis D virus infection.

[i] A serum pregnancy test will be performed at screening (i.e., within 7 days before the first study treatment administration on Cycle 1 Day 1) and at the Day 28 Follow-up Visit and 120 days after the last dose of atezolizumab follow-up visit. In addition, a urine pregnancy test should be done every 6 weeks from Cycle 3 Day 1 (i.e., urine pregnancy test will be performed on Day 1 of Cycles 3, 5, 7, 9, etc.), discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[j] Administration of *simlukafusp alfa*: the dose of *simlukafusp alfa* will remain consistent as long as it is tolerated by the participant (i.e., there is no up-titration in the Q3W dosing schema).

[k] Blood samples for baseline biomarker assessments have to be taken before study treatment administration on Cycle 1 Day 1. "FACS Basic" includes analysis of T, B, and NK cell numbers; and "FACS Advanced" includes analysis of T_{reg} as well as T-cell proliferation and differentiation.

[l] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of a Grade $\geq$ 3 IRR.

[m] On Cycle 2 Day 8 (+2/-1 day[s]) PD samples need to be taken prior to the fresh biopsy, on the same day.

[n] Tumor biopsies: A mandatory archival tumor tissue sample is to be obtained from all participants within 2 months after enrollment. Two fresh tumor biopsies, one *mandatory* at baseline (once eligibility has been confirmed, exception Cohort E as stated below) and one *optional* on-treatment at Cycle 2 Day 8 (+2/-1 day[s]), will be collected. For Cohort E only: Local confirmation of PD-L1 expression on archival tissue (or fresh biopsy if archival tissue not available). Central confirmation of PD-L1 expression required for unavailable local test. For Cohort E only, PD-L1 high status (i.e., TPS $\geq$ 50%) is required to confirm eligibility; therefore, an archival specimen containing adequate viable tumor tissue to establish PD-L1 expression status is required. If archival tissue is not available, PD-L1 will be performed on a fresh tumor biopsy which will also be used as the baseline biopsy if the participant is enrolled (i.e., a repeat biopsy is not necessary). Study Part III Cohorts G, H, K and L only: For participant's presenting with a single target lesion, which also is the only biopsiable one, no biopsies should be performed. For all cohorts, additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected in any participant, at the Investigator's discretion, to characterize the participant's response to treatment.

[o] Optional biopsy of progressing and/or regressing lesions is desirable at the investigator's discretion, to characterize the participant's response to treatment. If the participant progresses and discontinues treatment before the scheduled biopsy timepoint the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced, and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[p] Tumor assessment will be assessed at screening and every 8 weeks ($\pm$7 days) after study treatment for the first year. After the first year, in all cohorts except Cohort D, tumor assessments should be assessed every 12 weeks ($\pm$ 7 days); in Cohort D, tumor assessments should continue every 8 weeks ($\pm$7 days). Assessments continue until disease progression.

[q] Serum TSH level will be assessed at screening and on study (every 9 weeks from Cycle 1, Day 1). In case of abnormalities, the participant should be monitored until full resolution and further analysis (i.e., T3 and T4 serum level) performed. An endocrinologist should be consulted if an endocrinopathy is suspected.

[r] The autoantibody panel will be assessed at screening and as clinically indicated. In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment, the auto-antibody panel should be repeated. Participants with confirmed positive serology of at least one of the parameters in the autoantibody panel during the course of the study should be discussed between Sponsor and Investigators and, if judged clinically relevant, could be referred to a specialist to exclude an underlying autoimmune disease.

[s] Survival Follow-Up: Every 3 months ($\pm$ 30 days), starting at Day 120 visit ($\pm$30 days) the sites will provide the Sponsor an update on the survival status of each participant enrolled in the study. Post-study anti-cancer therapies should be collected and reported as appropriate in the eCRF.

Table 5 Schedule of Activities – Parts I, II, and III Q3W Scheme (Cycles 4+) (Cont.)

[t] SAEs occurring after signature of informed consent but before the first infusion of study treatment are reportable according to local regulations. SAEs related to study procedures are reportable after signature of informed consent. For SAEs before first dose, the corresponding AE page should also be completed

[u] In case *simlukafusp alfa* administration is omitted on Cycle 2 Day 1 the *optional* on-treatment tumor biopsy will be collected 7 days (+2/-1 day[s]) after the participant receives the next *simlukafusp alfa* dose administration in the upcoming cycle using an unscheduled kit. In such a case, PD samples (PD FACS Basic, PD FACS Advanced and PD Plasma) also will be collected on the day of the tumor biopsy using an unscheduled kit, while PD Serum is not collected (as not part of unscheduled kit).

Table 6 Schedule of Activities – Parts I, II, and III Q3W Scheme (Hourly)

Cycle	Day	Scheduled Time (h)	Time Window	Vital Signs [a]	12-lead ECG [b]	Routine Laboratory			*Simlukafusp alfa*		Atezolizumab		PD Sample (FACS)		PD Sample		Tumor Biopsy
						Hema [c]	Chem [c]	Coag [c]	PK [d]	ADA [e]	PK	ADA	Basic [f]	Adv [f]	Plasma [f]	Serum	
Cycle 1	1	Predose A+F	-4h	x	x	x[c]	x[c]	x[c]	x	x	x	x	x	x	x[g]	x[g]	
		EOI+0.5 A	±5min								x						
		1 F	±5min						x								
		EOI F	±15min	x	x				x								
		EOI+2 F	±30min	x					x								
		EOI+6 F	±30min	x					x								
		EOI+8 F	±30min	x													
	2	24 F	±2h	x		x	x	x	x						x	x	
	3 [h]	48 F	-2h/+48h	x		x	x		x								
	5 [h]	96 F	-2h/+48h	x		x	x										
	8	168 F	-2h/+48h	x		x	x	x	x		x		x	x	x	x	
Cycle 2	1 (±3)	Predose A+F	-4h	x		x[c]	x[c]	x[c]	x	x	x	x	x	x	x	x	
		EOI F	±15min	x					x								
		EOI+2F	±30min	x													
	2	24 F	±2h	x		x	x								x		
	3	48 F	-2h/+48h	x		x	x										
	8	168 F	-2h/+48h	x		x	x	x					x[i]	x[i]	x[i]	x[i]	x[n]
Cycle 3	1 (±3)	Predose A+F	-4h	x	x	x[c]	x[c]	x[c]	x	x	x	x	x	x	x	x	
		EOI F	±15min	x	x				x								
		EOI+2 F	±30min	x					x								
		EOI+6 F	±30min	x					x								
	2	24 F	±2h	x		x	x		x								
	3	48 F	-2h/+48h	x		x	x		x								
	8	168 F	-2h/+48h	x		x	x	x	x				x		x	x	
Cycle 4	1 (±3)	Predose	-4h	x		x[c]	x[c]	x[c]	x	x	x	x	x	x	x	x	
		EOI F	±15min	x													
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x								x		
	3	48 F	-2h/+48h	x		x	x										
	8	168 F	-2h/+48h	x		x	x	x					x				
Cycle 5	1 (±3)	Predose	-4h	x		x[c]	x[c]	x[c]	x	x	x	x					
		EOI F	±15min	x					x								

Table 6 Schedule of Activities – Parts I, II, and III Q3W Scheme (Hourly) (Cont)

Cycle	Day	Scheduled Time (h)	Time Window	Vital Signs [a]	12-lead ECG [b]	Routine Laboratory			*Simlukafusp alfa*		Atezolizumab		PD Sample (FACS)		PD Sample		Tumor Biopsy
						Hema [c]	Chem [c]	Coag [c]	PK [d]	ADA [e]	PK	ADA	Basic [f]	Adv [f]	Plasma [f]	Serum	
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x										
Cycle 6	1 (±3)	Predose	-4h	x		x[c]	x[c]	x[c]					x	x	x	x	
		EOI F	±15min	x													
		EOI+2F	±1h	x													
	2	24 F	±2h	x		x	x										
Cycle 7	1 (±3)	Predose	-4h	x		x[c]	x[c]	x[c]									
Cycle 8	1 (±3)	Predose	-4h	x		x[c]	x[c]	x[c]									
Subsequent Cycles	1 (±3)	At visit		x		x[c]	x[c]	x[c]					x[k]	x[k]	x[k]	x[k]	x[k]
Every TA[l]	1 (±3)	Predose	-4h						x[e,l]	x[e]	x[m]	x[m]					
		EOI F	±15min						x[l]								
		EOI+2F	±1h						x[l]								
Discontinuation		At visit		x	x	x	x	x	x	x	x	x					
28-Day F/U Visit		At visit		x	x	x	x	x	x	x	x	x	x		x	x	
3-month Safety F/U		At visit		x		x	x	x	x	x			x		x		
120 (± 30) days after last dose of atezolizumab		At visit		x		x	x	x		x	x	x	x		x		

Abbreviations: A = atezolizumab; ADA = anti-drug antibody; Adv = Advanced; AE = adverse event; Chem = blood chemistry; Coag = coagulation; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; F = *simlukafusp alfa* (FAP-IL2v); FACS = fluorescence-activated cell sorting; F/U = follow-up; h = hour; Hema = hematology; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IRR = infusion/injection-related reaction; PD = pharmacodynamics; PK = pharmacokinetic; TMB = tumor mutation burden; TA = tumor assessment.

[a] Vital signs (including seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate and body temperature; with pulse oximetry at the times indicated in the table, as per Table 11 for *simlukafusp alfa* and as per Table 12 for atezolizumab. Vital signs should be measured within 60 minutes prior to the atezolizumab infusion.

[b] Single 12-lead ECG will be obtained at screening, at pre-infusion and end of infusion on Cycle 1 Day 1 and Cycle 3 Day 1, at treatment discontinuation and at the 28-day Safety Follow-up Visit. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. Recording must be done prior to vital sign measurement and blood sampling.

[c] Hematology, blood chemistry, and coagulation can be performed up to 72 hours prior to scheduled dosing as results must be available before dosing. Additional blood samples for hematology, blood chemistry, and coagulation parameters will be taken as specified in this table and at the time of an IRR or hypersensitivity reaction. A lipid panel is to be obtained at screening and then every 9 weeks.

[d] Additional PK samples will be taken if a participant withdraws or has an IRR or an AE leading to dose reduction or delay of *simlukafusp alfa* administration. During the course of the study, PK/PD sampling timepoints may be modified based on emerging data to ensure that PK/PD of *simlukafusp alfa* can be adequately characterized. In this case, no new additional PK/PD samples will be introduced but sampling times may be modified or reduced.

Table 6 Schedule of Activities – Parts I, II, and III Q3W Scheme (Hourly) (Cont)

[e] Blood for ADA *simlukafusp alfa* determination will be taken on Cycle 9 Day 1 and at Cycle 13 Day 1. Afterwards, samples will be taken on Day 1 in cycles when a tumor assessment is performed. Blood for ADA determination with a corresponding PK sample should always be taken pre-dose. Additional samples for ADA *simlukafusp alfa* and PD sample (Plasma) will be taken at the time of an IRR or of hypersensitivity reaction for analysis of IgE/tryptase and ADA (Table 8), at treatment discontinuation (ADA only) and 120 days follow up.

[f] Blood for PD Sample (Plasma) will be collected in addition at the time of an IRR, and PD Sample for (FACS) Basic and (FACS) Advanced will be collected at the time of an Grade ≥ 3 IRR.

[g] Part III only: On Cycle 1 Day 1 an additional PD plasma and PD serum sample will be collected to allow for central laboratory virus testing (EBV, HPV)

[h] The time windows should be used for flexibility but the visits should not be merged. For example, if dosing occurs on a Thursday, to avoid a weekend visit, the Day 3 could be conducted on the following Monday and the Day 5 on the Wednesday.

[i] On Cycle 2 Day 8 (+2/-1 day[s]), PD samples need to be taken prior to the *optional* fresh biopsy, on the same day.

[j] Flexibility of +2/-1 day[s] aligned with biopsy

[k] Optional biopsy of progressing and/or regressing lesions is desirable at the investigator's discretion, to characterize the participant's response to treatment. If the participant progresses and discontinues treatment before the scheduled biopsy timepoint, the tumor biopsy should be taken at the time of treatment discontinuation. PD Sample (FACS) Basic, PD Sample (FACS) Advanced, and PD sample (plasma) should be taken in addition on the same day as the biopsy.

[l] A PK sample must be taken on Cycle 9. Afterwards, samples will be taken on Day 1 in cycles when the tumor assessment is performed.

[m] PK Atezolizumab and ADA Atezolizumab samples will be taken on Cycle 8 Day 1 then every 8 cycles from this timepoint onwards

[n] In case *simlukafusp alfa* administration is omitted on Cycle 2 Day 1, the on-treatment tumor biopsy will be collected 7 days (+2/-1 day[s]) after the participant receives the next *simlukafusp alfa* dose administration in the upcoming cycle using an unscheduled kit. In such a case, PD samples (PD FACS Basic, PD FACS Advanced and PD Plasma) also will be collected on the day of the tumor biopsy using an unscheduled kit, while PD Serum is not collected (as not part of unscheduled kit).

Table 7 Schedule of Activities – Part I Best Standard of Care (Cohort D Control Arm) Scheme

		Treatment Period				
Cycle	Screening/ Baseline	Cycle 1	Cycle ≥2	Discontinuation	28-Day Follow-up Visit (±3)	3-Month Safety Follow-up (±7 days)
Day	-28 to -2	1	1 (±5 days)			
Informed Consent [a]	x					
Demography	x					
Medical History	x					
Physical Examination [b]	x	x	x	x	x	x
ECOG Performance Status/ KPS [c]	x	x	x	x	x	x
Vital Signs [d]	x	x	x	x	x	x
Spirometry [e]	x					
12-lead ECG [f]	x	x	x [f]	x	x	
Hematology [g]	x	x	x	x	x	x
Blood Chemistry [g]	x	x	x	x	x	x
Lipid Panel [g]	x					
Coagulation [g,h]	x	x	x	x	x	x
Viral Serology [i]	x					
Urinalysis [g]	x	x	x	x	x	x
Pregnancy Test [j]	x		x [j]	x	x	
Echocardiography (TTE/MUGA)	x			x		
Study Drug Administration [k]		x	X			
PD Sample (FACS) Basic		x [l]				
PD Sample (FACS) Advanced		x [l]				
PD Sample (Plasma)		x [l]				
PD Sample (Serum)		x [l]				
Clinical Genotyping [m]	x					
Archival Tumor Tissue [n]	x					
Tumor Biopsy [n]	x		x [n]			
Tumor Mutation Burden (Plasma) [l]		x				
Tumor Assessment [o]	x		x [o]			
Pre-Study CT scan [p]	x					
Chest x-ray [q]	x					
Serum Thyroid-Stimulating Hormone [r]	x					
Autoantibody Panel [s]	x					
Survival Follow-Up [t]						x
Post-study Anticancer therapies [t]				x	x	x

Table 7 Schedule of Activities – Part I Best Standard of Care (Cohort D Control Arm) Scheme (Cont)

Cycle	Screening/ Baseline	Treatment Period		Discontinuation	28-Day Follow-up Visit (±3)	3-Month Safety Follow-up (±7 days)
		Cycle 1	Cycle ≥2			
Day	-28 to -2	1	1 (±5 days)			
Adverse Events [u]	x	x	x	x	x	x
Previous & Concomitant Treatments	x	x	x	x	x	x

Abbreviations: AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FACS = fluorescence-activated cell sorting; FEV = forced expiratory volume; FVC = forced vital capacity; IMP = investigational medicinal product; INR = international normalized ratio; IRR = infusion/injection-related reaction; KPS = Karnofsky Performance Score; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scans; PD = pharmacodynamic; PT = prothrombin time; PTT = partial prothrombin time; Q2W = every 2 weeks; Q3W = every 3 weeks; SAE = serious adverse event; SmPC = summary of product characteristics; TSH = thyroid stimulating hormone; TTE = transthoracic echocardiogram.

[a] Informed consent must be obtained before any study-specific procedures. The screening window clock starts with the first study-specific screening test or evaluation and not the consent date.

[b] Physical examinations (including weight) will be done at screening and prior to study treatment administration on infusion days. Height is to be measured at screening only.

[c] ECOG Performance Status/KPS will be done at screening, prior to each study treatment administration, and as specified in this table. On dosing days, results may be obtained up to 72 hours prior to study treatment administration.

[d] Vital signs include seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature. During infusions, vital signs are not required to be captured in the eCRF, unless abnormalities are observed. Participants experiencing Grade ≥3 vital sign abnormalities at a previous cycle should stay at the site after the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[e] Spirometry (FEV and FVC) will be performed at screening and as clinically indicated. Participants experiencing Grade ≥3 FEV decrease at a previous cycle should stay at site at the next study treatment administration for continued monitoring for a period deemed necessary by the investigator.

[f] Single 12-lead ECG recordings (i.e., qualitatively acceptable ECGs without artifacts) must be obtained on-treatment on Cycle 3 Day 1 and as clinically indicated. ECGs should be performed before any scheduled vital sign measurements and blood draws.

[g] Hematology, blood chemistry, coagulation, and urinalysis can be performed up to 72 hours before scheduled dosing as results must be available before dosing. A lipid panel is to be obtained at screening and then every 9 weeks. In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

[h] For coagulation (including PT, INR, and PTT), an additional sample will be taken at the time of an IRR or hypersensitivity reaction, and as clinically indicated. Additional coagulation parameters (i.e., anti-thrombin III, fibrinogen, prothrombin time, fibrin degradation products, D-dimer) may be assessed according to clinical judgment.

[i] A sample will be taken for serology for HIV, hepatitis A, B (HBsAg and HBcAb status), C and E at screening and as clinically indicated in case of suspicion of a viral infection. Exclusion of patients with active hepatitis B is considered sufficient to exclude all patients with a potential active hepatitis D virus infection.

[j] A serum pregnancy test will be performed at screening (within 7 days before the first administration of study treatment on Cycle 1 Day 1), on study as per relevant local guidelines and SmPC management for chemotherapy while receiving the IMP. For female participants of childbearing potential, the pregnancy test will be conducted at the treatment discontinuation visit and the Day 28 Follow-up Visit. Pregnancy tests during follow-up do not require on-site visits; results from treating physician can be used. In addition, a urine pregnancy test should be performed on Day 1 of every cycle from Cycle 3 Day 1, discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[k] Single agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine) will be administered per relevant local guidelines and SmPC management. Chemotherapy cycles may be 3-weekly or 4-weekly as defined in the SmPC.

[l] PD samples are to be collected predose.

Table 7 Schedule of Activities – Part I Best Standard of Care (Cohort D Control Arm) Scheme (Cont)

[m] Clinical genotyping: A mandatory whole blood sample for DNA analysis will be taken any time after eligibility has been confirmed. If this sample is missed, it can be collected at any other scheduled visit but not later than 3 weeks post enrollment.

[n] Tumor biopsies: A mandatory archival tumor tissue sample is to be obtained from all participants within 2 months after enrollment. A mandatory fresh tumor biopsy at baseline will be collected once eligibility has been confirmed. Additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected at the Investigator's discretion, to characterize the participant's response to treatment.

[o] Tumor assessment will be assessed at screening and every 8 weeks (±7 days) after study treatment, until disease progression or study treatment discontinuation, whichever occurs last. Participants who progress on chemotherapy treatment (i.e., gemcitabine or vinorelbine) have the opportunity to crossover to Arm 1 or Arm 2 and receive *simlukafusp alfa* in combination with atezolizumab (Q2W or Q3W, respectively). The decision to crossover will be taken after discussion between the Sponsor and the investigator.

[p] Optional latest pre-study or historical CT/MRI scan should be provided for assessment of TGK (within 12 weeks of Cycle 1 Day 1).

[q] Chest x-ray will be performed at screening (to obtain the baseline) and as clinically indicated during the study treatment period.

[r] Serum TSH level will be assessed at screening and on study (every 8 weeks from Cycle 1, Day 1). In case of abnormalities, the participant should be monitored until full resolution and further analysis (i.e., T3 and T4 serum level) performed. An endocrinologist should be consulted if an endocrinopathy is suspected.

[s] The autoantibody panel will be assessed at screening and as clinically indicated. In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment, the auto-antibody panel should be repeated. Participants with confirmed positive serology of at least one of the parameters in the autoantibody panel during the course of the study should be discussed between Sponsor and Investigators and, if judged clinically relevant, could be referred to a specialist to exclude an underlying autoimmune disease.

[t] Survival Follow-Up: Every 3 months (starting at Day 120 visit ±30 days), the sites will provide the Sponsor an update on the survival status of each participant enrolled in the study. Post-study anti-cancer therapies should be collected and reported as appropriate in the eCRF.

[u] SAEs occurring after signature of informed consent but before the first infusion of study treatment are reportable according to local regulations. SAEs related to study procedures are reportable after signature of informed consent. For SAEs before first dose, corresponding AE page should also be completed.

Table 8 Schedule of Activities for Infusion-Related Reactions and Other Unscheduled Visits (All Parts)

		Scheduled Time	PK Sample	Blood for PD Sample (Plasma)[a]	PD Sample (FACS) Basic and Advanced	IgE and Tryptase[b]	ADA	Hematology	Serum Chemistry[c]	Coagulation
Grade 2 IRR	Unscheduled Visit	At the time of IRR	x	x		x	x	x	x	x
Grade ≥ 3 IRR or Anaphylaxis	Unscheduled Visit	At the time of IRR	x	x	x	x	x	x	x	x
Other Unscheduled Visit	Unscheduled Visit	Anytime	x	x	x		x	x	x	x

Abbreviations: ADA = anti-drug antibody; h = hour; Ig = immunoglobulin; IRR = infusion/injection-related reaction; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Sample for cytokine assessment and soluble CD25.

[b] For participants who experience a Grade ≥ 3 IRR during the first study treatment administration, tryptase and total IgE samples should be collected and analyzed both locally and centrally, prior to the next study treatment administration. For participants who experience a Grade ≥ 2 IRR for the first time with the second or subsequent study drug infusion, tryptase and total IgE samples should be collected and analyzed locally and centrally. If tryptase and/or IgE are elevated, collect a second sample for IgE/tryptase local and central analysis at least 48 hours from onset of the reaction to rule out the possibility of an anaphylactic reaction.

Note: IgE and Tryptase samples should always be collected for local and central assessments when samples are required.

[c] Creatinine clearance not required.

2. INTRODUCTION

2.1 STUDY RATIONALE

Simlukafusp alfa, also known as RO6874281 is a fibroblast activation protein-α (FAP)-targeted novel, monomeric, tumor-targeted interleukin (IL)-2 variant (IL-2v) immunocytokine developed to overcome the limitations of wild-type IL-2 by activating immune effector cells and selectively promoting immune responses in the microenvironment of the tumors that overexpress FAP. FAP, also known as seprase, is a dimeric Type II transmembrane glycoprotein with proteolytic activity and has been identified as a promising target for tumor treatment. It is highly expressed on cancer-associated stroma cells of >90% of human epithelial malignancies, particularly on the cell surface of tumor stromal fibroblasts and activated cancer-associated fibroblasts and pericytes. FAP is also expressed in diseases such as rheumatoid arthritis, osteoarthritis, cirrhosis, and pulmonary fibrosis and in tissues that undergo remodeling (Brennen et al. 2012; Liu et al 2012) (for more details see Section 2.3 of the *Simlukafusp Alfa* Investigator's Brochure).

In many tumor types where FAP expression is highly prevalent some participants derive benefit from treatment with anti-programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies. In addition to its stimulatory effects on immune effector cells at the site of disease, *simlukafusp alfa* may broaden and further enhance the quality, depth, and duration of anti–PD-1/PD-L1 antibody effects specifically in tumor-infiltrating lymphocytes. Those immunostimulatory effects of *simlukafusp alfa* are expected to occur in all participants independent of the type of previous treatment.

PD-L1 expression is prevalent in many human tumors. Elevated PD-L1 expression is associated with a poor prognosis in participants with non-small cell lung cancer (NSCLC; Mu et al. 2011) and other solid tumors (Thompson et al. 2006; Hamanishi et al. 2007; Hino et al. 2010). In mouse tumor models, interruption of the interaction between PD-L1 and PD-1 resulted in antitumor effects (Iwai et al. 2002; Strome et al. 2003). In a Phase Ia dose-escalation study with atezolizumab, confirmed responses (complete and partial responses [PR]) were observed in 18% of 175 efficacy-evaluable participants with advanced solid tumors, including 21% of participants with NSCLC and 26% of participants with melanoma (Herbst et al. 2013). Atezolizumab is being studied in multiple clinical settings and is currently approved for treatment of participants with metastatic NSCLC who have disease progression during or after platinum-containing chemotherapy (Tecentriq Package Insert). Participants with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on an U.S. Food and Drug Administration (FDA)-approved therapy for these aberrations before receiving atezolizumab. Additionally, *atezolizumab is approved for the treatment of urothelial carcinoma, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.*

This study is a basket trial, designed to confirm the hypothesis that immune-cell activation by *simlukafusp alfa* improves clinical activity of atezolizumab over a range of advanced and/or metastatic solid tumors.

Biologically, the combination of the mechanisms of action of IL-2 and checkpoint inhibitors (CPIs) is central to this study. The combination of *simlukafusp alfa* and atezolizumab represents the denominating therapeutic backbone across all disease indications of the study. However, for a specific disease setting (e.g., frontline setting, previously untreated patients), requirements towards the therapeutic scaffold may differ. Additional therapeutic partners may be needed to warrant investigation in such settings. Therefore, the study design allows the introduction of additional treatments, as well as *simlukafusp alfa* + atezolizumab, where it is necessitated by standard of care of a given disease setting. *simlukafusp alfa* + atezolizumab in combination with other therapeutic agents (*simlukafusp alfa* + atezolizumab + drug X) in specific indications may be investigated, where it is clinically warranted and supported by data. Those disease indications with extended treatment scaffolds will be opened through a substantial amendment.

The scientific rationale for the study design is provided in Section 4.3.

2.2 BACKGROUND

Cancer remains a major cause of death worldwide despite several new agents providing survival benefits to patients. The management of most advanced solid tumors remains challenging because of the high rate of tumor recurrence or the development of metastases associated with poor prognosis. Advances in the understanding of molecular cancer biology have led to significant progress in the diagnosis and therapy of cancer, but there is still a high unmet medical need for more effective therapies.

Simlukafusp alfa is a novel immunocytokine, designed to increase the benefit-risk ratio of systemic IL-2 therapy. It combines both a tumor-specific antibody against FAP for targeting (i.e., anchoring) and an engineered IL-2 cytokine (IL-2v) for improved tolerability. *Simlukafusp alfa* delivers immune modulatory activity to natural killer (NK) and T-cell subsets to effectively mobilize and sustain antitumor immune responses at tumor sites. Compared with High-Dose IL-2 therapy, the improved overall tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profile of *simlukafusp alfa* allows investigation of this compound for clinical benefit in a broad population of advanced and metastatic cancer participants.

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody which targets PD-L1 on immune cells or tumor cells and prevents interaction with either PD-1 receptor or B7.1 (*also known as* CD80), both of which function as inhibitory receptors expressed on T cells. PD-L1 expression is prevalent in many human tumor types, including but not limited to NSCLC, bladder cancer, and melanoma. Elevated PD-L1 expression can be predictive for atezolizumab benefit (Fehrenbacher et al. 2016).

Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell responses through increased T-cell priming, expansion, and/or effector function.

In preclinical models, *simlukafusp alfa* has demonstrated the potential to enhance those T-cell responses. In murine tumor models, the survival benefit of the combination of *simlukafusp alfa* with atezolizumab is established and superior to both antibodies when dosed individually.

Anti–PD-1/PD-L1 antibodies are effective treatment options for metastatic disease. FAP is found on cancer-associated stroma cells of >90% of human epithelial malignancies, particularly on the cell surface of tumor stromal fibroblasts and activated cancer-associated fibroblasts and pericytes. Immunohistochemical analyses confirmed high FAP expression in the stroma of various tumors, including major tumor entities such as breast, colorectal, lung, pancreatic, and gastric cancers, head and neck cancer, mesothelioma, and renal cell carcinoma (RCC) (for further information and detail please refer to the *Simlukafusp Alfa* Investigator's Brochure). FAP overexpression is found independently of the histologic subtype of the tumor (i.e., adenomatous, squamous, or mixed/other differentiation). High FAP expression is also found in cancer cells of mesenchymal lineage or may be aberrantly expressed in any cancer type. Hence, FAP-targeting allows the delivery of *simlukafusp alfa* to a broad spectrum of tumors.

In vitro and in vivo non-clinical pharmacology studies have demonstrated the ability of *simlukafusp alfa* to eliminate tumor cells. *Simlukafusp alfa* is differentiated from aldesleukin and first generation IL–2v-based immunocytokines by its superior tumor targeting, lack of preferential activation of regulatory T cells and reduced activation-induced cell death, as well as its strong expansion and activation of NK cells and CD8 T cells in tumors, peripheral blood, and lymphoid tissues. In addition, *simlukafusp alfa* strongly enhances in vivo therapeutic efficacy and/or survival mediated by antibody-dependent cellular cytotoxicity-competent or cytotoxicity-enhanced antibodies.

For further information and detail on the studies above and a detailed description of the chemistry, pharmacology, activity, and safety of *simlukafusp alfa*, please refer to the *Simlukafusp Alfa* Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

Studies evaluating the efficacy and safety of *simlukafusp alfa* in monotherapy (dose escalation part of Study BP29842), in combination with atezolizumab alone (BP40234, BP29842, and WO39608), in combination with atezolizumab and bevacizumab (BP39365), in combination with trastuzumab or cetuximab (BP29842), and in combination with pembrolizumab (BP41054) are ongoing at the time of protocol finalization.

Simlukafusp alfa is designed to improve the benefit-risk ratio of systemic IL-2 therapies through tumor targeting and abrogated CD25 binding. The safety profile of atezolizumab given as monotherapy in urothelial cancer and NSCLC is well-established and is considered acceptable.

Simlukafusp alfa has demonstrated single agent activity in the ongoing dose escalation part of Study BP29842, with some patients achieving durable responses. Clinical activity has been observed with some patients achieving durable responses as well as disease control with disease stabilization or minor response. Further, disease control with disease stabilization or minor response was achieved in other solid tumor types.

Review of safety data *from 445 patients (as of the Simlukafusp Alfa Investigator's Brochure data cut-off, 17 February 2020)* emerging from ongoing studies with *simlukafusp alfa* indicated that the majority of adverse events (AEs) were mild to moderate in severity (Grade 1 or 2) and included pyrexia, chills, fatigue, decreased appetite, asthenia, nausea, vomiting, diarrhea, rash, *pruritus,* IRR, anemia, hypotension and liver function test (LFT) abnormalities, occurring in ≥20% of the patients overall. *Grade 3 - 4 AEs reported from more than 5% of patients were aspartate aminotransferase increased (9.2%), alanine aminotransferase increased (8.5%), gamma-glutamyltransferase increased (8.3%), anemia (10.8%), lymphopenia (8.8%), hypophosphatemia (8.3%), IRR (5.8%) and pyrexia (5.4%). Two treatment-related Grade 5 events were reported; these were events of pneumonitis and general physical health deterioration.*

Identified risks with *simlukafusp alfa* include pyrexia, infusion/injection-related reaction (IRR), capillary leak syndrome (CLS), and liver function test (LFT) abnormalities. Furthermore, based on the analysis of concomitant elevations of liver enzyme and bilirubin (Hy's law cases) in patients receiving the combination of *simlukafusp alfa* and atezolizumab, a new risk of overlapping toxicity for liver effects was identified. In addition, an event of Stevens-Johnson syndrome (SJS) occurred in a patient receiving *simlukafusp alfa* in combination with atezolizumab in study BP40234, where the contributory role of *simlukafusp alfa* and/or atezolizumab was considered: severe skin toxicity is a known IL-2 mediated effect, and has also been described as a*n identified* risk with atezolizumab. Due to: (1) lack of a clear causal association between the study medications and SJS in the presence of strong confounders, (2) overall emerging safety profile from ongoing clinical development; the contribution of *simlukafusp alfa* to SJS is uncertain. In the presence of observed initial clinical activity, the Sponsor therefore is of the opinion that the potential benefit of *simlukafusp alfa* in combination with CPI treatment, i.e. atezolizumab in Study BP40234 outweighs the risks of potential severe cutaneous adverse reactions, also in patients who are CPI naïve.

Guidelines for timely intervention and treatment of the identified and potential risks with *simlukafusp alfa* and atezolizumab as well as inclusion/exclusion criteria have been implemented in the protocol to mitigate the risks and to ensure a positive benefit risk.

The mild to moderate severity of most frequently reported events, the acceptable rate of AE-driven treatment discontinuations attributable to *simlukafusp alfa* and or combinations, the frequency of treatment-related Grade 3/4 events, and existing risk management guidelines in place, when taken together, ensure that the observed benefits thus far outweigh the risks.

Management guidelines for the identified and potential toxicities are provided in the protocol. For more details, see the *Simlukafusp alfa* Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 9.

Table 9 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate antitumor activity of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in comparison with the SoC in participants with advanced/and or metastatic solid tumors	• ORR according to RECIST v1.1
Secondary	
• To further characterize the antitumor activity of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in participants with advanced/and or metastatic solid tumors relative to SoC.	• DCR • DoR • PFS • OS, if data are mature at the time of analysis [a]
• To evaluate the safety and tolerability of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs	• Incidence of and severity of AEs • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results
• To determine the relevance of the baseline tumor PD-L1 status for treatment benefit	• PD-L1 status by immunohistochemical methods
• To characterize in tumor samples treatment-induced PD effects of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs	• Change from baseline in density (cell/mm2) of CD8+ and CD3-perforin+ cells, and PD-L1 by immunohistochemical methods

Table 9 Objectives and Endpoints (cont.)

Objectives	Endpoints
Tertiary/Exploratory	
• To characterize the antitumor activity of *simlukafusp alfa* in combination with atezolizumab and potentially other drugs according to iRECIST	• ORR, DCR, DoR, PFS according to iRECIST
• To characterize the PK of *simlukafusp alfa*, when used in combination with atezolizumab and potentially other drugs	• CL and V
• To characterize the immunogenicity profile of *simlukafusp alfa* when used in combination with atezolizumab and potentially other drugs	• Incidence of ADAs.
• To investigate treatment-induced PD effects of the study treatment with *simlukafusp alfa* in combination with atezolizumab and potentially other drugs on peripheral blood lymphocytes, soluble markers, and tumor microenvironment.	• Tumor tissue samples: • FAP expression, MMR/MSI status, gene expression profile, at baseline and on treatment • Whole blood samples: • Change from baseline in the following cell subsets: CD4+ T cells, CD8+ T cells, NK cells, monocytes and T_{reg} cells, B cells, effector TEM and proliferating T cells • Determinants of autoimmunity (e.g., KIR-HLA mismatch) and whole genome sequencing • Plasma/serum samples: • Soluble CD25 • Cytokines and inflammation markers (which may include but are not limited to TNF-α, IFN-γ, CRP, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12) • Soluble circulating FAP • Tumor mutation burden

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CL = clearance; CRP = c-reactive protein; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; FAP = fibroblast activation protein-α; IFN-γ = interferon gamma; IL-2 = interleukin 2; IL-4 = interleukin 4; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-10 = interleukin 10; IL-12 = interleukin 12; HLA = human leukocyte antigen; iRECIST = modified RECIST v1.1 for immune-based therapeutics; KIR = killer cell immunoglobulin-like receptor; MMR = mismatch repair genes; MSI = microsatellite instability; NK = natural killer; PD = pharmacodynamic; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors; SoC = standard of care; TEM = memory T cells; TNF-α = tumor necrosis factor alpha; T_{reg} = regulatory T cell; V = volume of distribution.

[a] For Part I Cohort D, OS will not be analyzed due to crossover.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, multicenter, basket trial Phase II, clinical study to evaluate the antitumor activity of *simlukafusp alfa* in combination with atezolizumab over a range of advanced and/or metastatic solid tumors. This study is adaptive in nature, and is a multiple-part study.

An overview of the study design is provided in Section 1.2.

Simlukafusp alfa in combination with atezolizumab may deliver improved clinical benefit for participants as compared with CPI monotherapy. CPI therapy is also being explored in combination with other drugs. While *simlukafusp alfa* + atezolizumab is the backbone investigated in this basket trial, *simlukafusp alfa* has the potential of being combined with other partners. On the basis of data from ongoing combination studies of *simlukafusp alfa* and atezolizumab, additional combination therapies (*simlukafusp alfa* + atezolizumab + drug X) may be proposed and added to this study protocol via an amendment.

There are currently two treatment schedules in the protocol:

- Once weekly (QW)/every 2 weeks (Q2W) schedule (induction/maintenance): *simlukafusp alfa* QW + atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* + atezolizumab Q2W, thereafter
- Every 3 weeks (Q3W) schedule: *simlukafusp alfa* + atezolizumab Q3W

For all cohorts, the actual number of participants enrolled may be increased to ensure that the necessary numbers of response-evaluable participants presented below are obtained (see Section 8.6.2 and Section 9.2).

4.1.1 Part I

In Part I, approximately 220 response-evaluable participants with advanced and/or metastatic NSCLC after at least one previous regimen of anticancer therapy for metastatic disease will be divided into the following cohorts:

- Cohort A: CPI-naïve participants (20 response-evaluable participants), optional biopsies
- Cohort B: CPI-experienced participants (20 response-evaluable participants), mandatory biopsies
- Cohort C: Contingent upon the confirmation of the treatment's safety and preliminary activity analysis, a mandatory biopsy cohort may be introduced to enroll 20 response-evaluable CPI-naïve NSCLC participants.
- Cohort D: Contingent upon the confirmation of the treatment's safety and preliminary activity analysis of Cohort B, a cohort may be opened to enroll 120 randomized CPI-experienced participants. Participants in Cohort D must

have additionally experienced disease progression after or during docetaxel therapy; biopsies are mandatory

- Cohort F: CPI-experienced participants; platinum pre-treated (40 response-evaluable participants), mandatory biopsies

Participants in Cohorts A, B, and C will follow the QW/Q2W treatment schedule.

Participants in Cohort D will be randomized into three arms, as follows:

- Arm 1: *simlukafusp alfa* in combination with atezolizumab; QW/Q2W schedule
- Arm 2: *simlukafusp alfa* in combination with atezolizumab; Q3W schedule
- Arm 3: Control arm; single-agent chemotherapy with gemcitabine or vinorelbine

Participants in Arm 3 who experienced disease progression during or after gemcitabine chemotherapy in an earlier treatment line will receive vinorelbine; all other participants in Arm 3 will receive gemcitabine. There is paucity of clinical activity data of CPI treatment after previous exposure to a compound of the same drug class. Activity data from Arm 3 will allow interpreting the signals of Arm 1 and Arm 2 more robustly and increases the scientific value of the study.

Participants in Cohort D who are randomized to Arm 3 and who progress on chemotherapy treatment have the opportunity to crossover to Arm 1 or Arm 2 and receive *simlukafusp alfa* in combination with atezolizumab (QW/Q2W or Q3W). The decision to crossover is at the discretion of the investigator. Participants must have documented radiographic (or other imaging-based assessment) disease progression reported in the electronic case report form (eCRF). The Sponsor's approval based on the provided tumor assessment data is needed prior to crossover.

Participants in Cohort F will follow the Q3W treatment schedule.

4.1.2 Part II

In Part II, up to 80 response-evaluable participants with previously untreated driver-mutation negative advanced and/or metastatic NSCLC will be included. Participants must not have been exposed to any prior regimen of anticancer therapy (i.e., chemotherapy, mutation-targeted therapy and/or CPI therapy). Part II will consist of one cohort (Cohort E). This cohort will include only PD-L1 high participants (tumor proportion score [TPS] $\geq$50%, used interchangeably with tumor cell staining). Eligible participants will be randomized to either receive *simlukafusp alfa* QW/Q2W or Q3W in combination with atezolizumab Q2W or Q3W, respectively (see also Figure 2). Participants in Part II are required to provide a mandatory archival tumor tissue sample within 2 months after enrollment.

4.1.3 Part III

In Part III, approximately 160 response-evaluable participants with locally advanced or persistent or relapsed/recurrent and/or metastatic squamous cell carcinoma (SCC) will be divided into the following cohorts:

- Cohort G: CPI-naïve SCC of the head and neck (SCCHN) (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort H: CPI-experienced SCC of the head and neck (SCCHN) (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort I: Previously treated, CPI-naïve squamous esophageal cancer (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsies
- Cohort J: Previously treated, CPI-naïve squamous cervical cancer (20 response-evaluable participants), Q3W schedule, mandatory *pre-treatment* biopsy
- Cohort K: CPI-naïve SCCHN (20 response-evaluable participants), QW/Q2W schedule, 1L/1L+, mandatory *pre-treatment* biopsies
- Cohort L: CPI-experienced SCCHN participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies
- Cohort M: Esophageal SCC participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies
- Cohort N: Cervical SCC participants; QW/Q2W schedule, 2L/2L+, mandatory *pre-treatment* biopsies

In Part III, participants in Cohorts G-J will receive *simlukafusp alfa* Q3W in combination with atezolizumab Q3W and participants in Cohorts K-N will receive *simlukafusp alfa* QW in combination with atezolizumab Q2W for 4 weeks followed by *simlukafusp alfa* in combination with atezolizumab Q2W.

In any of the Part III cohorts, the sample size may be extended to a total of 80 participants in order to confirm clinical activity observed in the first 20 response-evaluable participants (see Section 9.2.3).

4.1.4 Additional Parts

Additional parts and cohorts (Part IV, Part V, etc.) may be opened at a later time investigating *simlukafusp alfa* in combination with atezolizumab and potentially other drugs in other tumor types selected on the basis of emerging data from this study or information deriving from other studies (via an amendment).

4.1.5 Length of the Study

The recruitment is expected to last approximately 19 months for Part I, approximately 8 months for Part II and approximately 18 months for Part III of the study.

Participants may continue study treatment for a maximum of 24 months. In case the participant has reached the defined duration and continues to derive benefit, a longer treatment duration might be granted by the Sponsor.

All participants will be treated with the study treatment, until disease progression, unacceptable toxicities, or withdrawal of consent. For participants who experience radiographic progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) during study, but have evidence of clinical benefit, there may be the possibility to continue on study after discussion between the Investigator and the Sponsor. In case one therapeutic agent is permanently discontinued, treatment with the other agent may be continued, provided:

- Participants are agreeable
- There is evidence of clinical benefit per the Investigator
- No signs/symptoms indicating unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status or Karnofsky Performance Score (KPS) attributed to disease progression
- No tumor growth at critical sites
- Participants with approved alternative therapies acknowledge where applicable via informed consent form (ICF)

Treatment will be continued until the participant is no longer experiencing clinical benefit or meets discontinuation criteria.

4.1.6 Stopping Rules Criteria

Parts I, II, and III (all cohorts) may be stopped for lack of activity or unacceptable safety. Refer to Section 9.5, interim analyses, for details.

4.2 JOINT MONITORING COMMITTEE

The Sponsor will form a Joint Monitoring Committee (JMC) to monitor participant safety throughout the study. The JMC will consist of designated Sponsor personnel, including a JMC Chair, clinical scientist, drug safety officer, biostatistician, and independent clinical expert(s) (i.e., expert[s] independent from the Sponsor).

The JMC will conduct an ongoing assessment of the incidence and nature of AEs, serious adverse events (SAEs), adverse events of special interest (AESI), frequency of death from all causes and clinically significant laboratory abnormalities. The JMC will also evaluate all clinically relevant toxicities that are known to be associated with

simlukafusp alfa and atezolizumab. The JMC will review all study data at regular intervals, as defined in the JMC charter.

At the time of each review, the JMC will make one of the following recommendations: the trial may continue unchanged, the trial is to be stopped, additional analyses are to be performed, enrollment is to be held pending further safety evaluations, or a protocol amendment is recommended. The JMC will report recommendations to the Sponsor.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

The QW/Q2W treatment schedule of this study consists of an induction phase and a maintenance phase (i.e., 4 times weekly administrations of *simlukafusp alfa* and two times once every 2 weeks administrations of atezolizumab in the induction phase, followed by biweekly administrations of *simlukafusp alfa* and atezolizumab in the maintenance phase). The Q3W treatment schedule of this study consists of a less frequent treatment interval with every 3 weeks administrations of *simlukafusp alfa* and atezolizumab. Rationale for the treatment schedule is provided in Section 4.4.

4.3.1 Rationale for Study Population

FAP is expressed in the stromal compartment of virtually all solid tumors (see Table 1 of the *Simlukafusp alfa* Investigator's Brochure). In many of those tumor types, some participants derive benefit from treatment with anti–PD-1/PD-L1 antibodies.

In addition to its stimulatory effects on immune effector cells at the site of disease, *simlukafusp alfa* may broaden and further enhance the quality, depth, and duration of anti–PD-1/PD-L1 antibody effects specifically in tumor-infiltrating lymphocytes. Those immunostimulatory effects of *simlukafusp alfa* are expected to occur in all participants independent of the type of previous treatment.

Anti–PD-1/PD-L1 antibodies are effective treatment options for metastatic disease. FAP is found on cancer-associated stroma cells of $>$90% of human epithelial malignancies, particularly on the cell surface of tumor stromal fibroblasts and activated cancer-associated fibroblasts and pericytes. Immunohistochemical analyses confirmed high-FAP expression in the stroma of various tumors, including major tumor entities such as lung, breast, colorectal, pancreatic, gastric cancers, head and neck cancer, mesothelioma, and RCC. FAP overexpression is found independently of the histologic subtype of the tumor (i.e., adenomatous, squamous, or mixed/other differentiation).

This Phase II study of *simlukafusp alfa*, in combination with atezolizumab, in participants with advanced and/or metastatic solid tumors is designed to confirm the hypothesis that immune-cell activation by *simlukafusp alfa* improves clinical activity of atezolizumab.

4.3.1.1 Part I

Part I is no longer enrolling participants, therefore, this section has not been updated as of protocol version 7.

Part I of this study will investigate the activity of the combination in NSCLC.

In 65% of primary NSCLC lesions (>90% in squamous and >45% in non-squamous carcinomas), the stromal component demonstrates FAP expression of moderate to high levels (see Table 1 of the *Simlukafusp alfa* Investigator's Brochure). Virtually all NSCLC lesions express FAP at least with low levels.

Currently, atezolizumab is approved for treatment of patients with metastatic NSCLC who have disease progression during or after platinum-containing chemotherapy and it is also being studied in other settings within the disease type of NSCLC (e.g., frontline setting in combination with chemotherapy).

Three objective responses were observed in 19 participants treated with the combination of cergutuzumab amunaleukin and atezolizumab. One participant with NSCLC (adenocarcinoma) achieved a complete remission (CR) of his disease after being on study for more than 30 weeks and sustained the response at the time of withdrawal after Week 49. Another participant with NSCLC has achieved a partial response (PR) with tumor reduction of -88% per RECIST v1.1 after being on treatment for 15 weeks and was treated for 15 months following treatment start. Another participant, previously treated with CPI, achieved a target-lesion shrinkage of 34% at Day 54.

Two participants achieved disease stabilization lasting more than 20 weeks. Three additional participants achieved disease stabilization over a shorter time period up to 12 weeks. In general, the AEs associated with the administration of cergutuzumab amunaleukin in combination with atezolizumab were manageable and the safety profile assessed in 49 participants enrolled into Study BP29435 was considered acceptable and consistent with those of IL-2 and atezolizumab therapies.

Those preliminary data further warrant the investigation of *simlukafusp alfa* in combination with atezolizumab in NSCLC.

Simlukafusp alfa has two potential dimensions of how it can deliver a favorable benefit/risk ratio to participants in combination with atezolizumab: firstly, it will be tested whether the combination has a broader response pattern than atezolizumab alone (Cohort A). This means, more participants in CPI-sensitive indications derive benefit from the combination. Secondly, it will be tested whether the combination renders CPI-refractory/unresponsive disease sensitive to study treatment (Cohort B). This means participants who have progressed on CPI treatment achieve at least disease control from the study treatment.

Participants who have progressed on platinum-based combination chemotherapy and who have received a CPI either as monotherapy or as part of a combination therapy frequently receive docetaxel as subsequent treatment. Docetaxel has demonstrated response rates of around 10%–15% after platinum doublet chemotherapy. After docetaxel failure, there is no effective treatment established. Gemcitabine or vinorelbine in that setting have demonstrate only low activity and other, more effective treatment options, in particular chemotherapy sparing approaches, will address a high unmet medical need.

An additional cohort (Cohort F), investigating another patient population (i.e., CPI-experienced, platinum-therapy experienced, docetaxel-naïve) has been added to explore the combination of *simlukafusp alfa* and atezolizumab in a Q3W schedule. This patient population is distinct from the front-line patient population in Cohort E (Part II) and the more heavily pre-treated population with prior docetaxel experience in Cohort D (Part I). Based on the outcome of Cohort F, this patient population would be considered for a future potential registrational trial.

4.3.1.2 Part II

Part II is no longer enrolling participants, therefore, this section has not been updated as of protocol version 7.

Despite improvements in the first-line treatment of participants with metastatic NSCLC that have resulted in longer survival times and reduced disease-related symptoms, significant unmet medical needs exist in this patient population.

Atezolizumab and pembrolizumab have shown comparable 12-month overall survival (OS) rates and objective response rates (ORRs) in previously untreated as well as in previously treated participants expressing high levels of PD-L1 on their tumors (Garon et al 2015; Garassino et al. 2016; Reck et al. 2016; Rittmeyer et al. 2017).

Cohort E is designed to compare the combination of *simlukafusp alfa* with atezolizumab in two different treatment regimens (QW/Q2W and Q3W) in participants with high tumor PD-L1 expression (TPS $\geq$50%). In addition, participants must not have received prior systemic therapy for metastatic NSCLC and have no target mutations and /or rearrangements (see Figure 2). This design is expected to allow for rapid signal detection in a homogeneous patient population. The requirement for participants to have a high level of PD-L1 expression is to ensure a population with a good probability of response.

Recently, immune CPI, including PD-L1/PD-1 blocking antibodies, have emerged as a new therapeutic option for the first-line treatment of metastatic NSCLC. Study KEYNOTE-024 was a Phase III, randomized, open-label study evaluating pembrolizumab given as monotherapy compared with platinum-based chemotherapy in participants who had previously untreated advanced NSCLC with PD-L1 expression on

at least 50% of tumor cells. In this study, median progression-free survival (mPFS) was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group (hazard ratio [HR] = 0.50; 95% CI: 0.37, 0.68; $p < 0.001$). The estimated rate of OS at 6 months was 80.2% (95% CI: 72.9%, 85.7%) in the pembrolizumab group versus 72.4% (95% CI: 64.5%, 78.9%) in the chemotherapy group; median OS was not reached in either group. OS was significantly longer in the pembrolizumab group than in the chemotherapy group (HR = 0.60; 95% CI: 0.41, 0.89; p = 0.005) (Reck et al. 2016). On the basis of this study, pembrolizumab was approved for the first-line treatment of metastatic NSCLC in participants whose tumors have high PD-L1 expression (TPS $\geq$ 50%) with no EGFR or ALK gene aberrations.

Data from Phase Ia study PCD4989g suggest that tumor PD-L1 status as determined by immunohistochemistry (IHC) in participants with NSCLC correlates with response to atezolizumab (see the Atezolizumab Investigator's Brochure for details on clinical activity in participants with NSCLC treated to date). Participants whose tumors were characterized as expressing high tumor cells or immune cells exhibited an ORR of 50% (TC3 or IC3 group; 11 of 22 participants; 95% CI: 28.2%, 71.8%). These data provide a rationale for evaluating the activity of atezolizumab in participants with Stage IV NSCLC selected on the basis of tumor PD-L1 expression.

The combination of PD-L1/PD-1 inhibitors with biologic agents, such as FAP-IL2v, is an attractive option. This is based on several hypotheses indicating that FAP-IL2v may augment immune-enhancing properties of CPIs by several mechanisms, including the expansion of effector cell populations (i.e., NK cells, cytotoxic T cells and the induction of a pro-inflammatory tumor microenvironment. Thus, atezolizumab and FAP-IL2v combined will be investigated in participants with untreated NSCLC with high PD-L1 expression to assess if this treatment combination induces tumor regression and prolongs OS.

4.3.1.3 Part III

SCCs are among the most prevalent human cancers. SCC comprises a wide range of tumors originated from diverse anatomical locations and represents a major cause of death worldwide. SCCs are classified according to the location where they appear, being frequently found in skin, head and neck, esophagus, lung and cervix and more rarely in pancreas, thyroid, bladder and prostate (Sánchez-Danés and Blanpain 2018).

Study BP29842 showed single-agent activity of *simlukafusp alfa* in cancers with squamous histology. A total of five participants with SCC were enrolled in this study of which one participant with SCCHN achieved a CR of his disease after being on the study for more than a year and sustained the response at the time of discontinuation when the maximum treatment duration of 24 months was reached. Three of those 5 participants have achieved disease stabilization (stable disease [SD]) of which one participant with penile SCC had a partial remission of his disease as per modified RECIST after being on

treatment for 1 year. From the 5 participants with SCC only, one participant presented a disease progression while being on the study.

Immunohistochemical analyses confirmed high FAP expression in the stroma of various tumors, including major tumor entities such as breast, colorectal, lung, pancreatic, and gastric cancers, head and neck cancer, mesothelioma, and RCC (see the *Simlukafusp alfa* Investigator's Brochure).

For analyzed cases of head and neck carcinomas, 90% of all primary tumor and 68% of all metastatic specimens showed strong or at least intermediate FAP immunoreactivity.

FAP has been reported to be present in the tumor stroma of epithelial cancers (including, for example, esophageal SCC [Tabola et al. 2017; Ha et al. 2014]) and also was discussed to play a role as an early marker of tumor invasion in squamous lesions of the uterine cervix (Jin et al. 2003). In general, physiological low FAP expression may be triggered by tissue remodeling processes operating in various tissues, including uterus and cervix (Jacob et al. 2012).

Tumor Indications to be *i*nvestigated in Part III

In Part III of this study, the following three tumor types will be investigated: SCCHN, squamous esophageal cancer, and squamous cervical cancer.

Squamous Cell Carcinoma Head and Neck (SCCHN)

Atezolizumab has shown encouraging activity in metastatic and recurrent SCCHN in Study PCD4989g. In a cohort of 32 efficacy-evaluable participant with SCCHN, the confirmed ORR was 22% (95% CI: 9.3%–40.0%), the mPFS was 2.6 months (range: 0.5–48.4 months), and the median OS was 6.0 months (range: 0.5–51.6 months, censored value). Encouraging response and long-term survival were shown in recurrent and metastatic SCCHN independently of PD–L1 IHC or human papilloma virus (HPV) status and warrant further investigation (Bahleda et al. 2017).

Furthermore the CPI pembrolizumab and nivolumab have shown activity in metastatic SCCHN in the second- and third-line setting and beyond (Chow et al. 2016; Ferris et al. 2016). Both nivolumab and pembrolizumab, which target PD-1, have been approved by the U.S. FDA for participants who have previously been treated for recurrent or metastatic SCCHN (Opdivo® U.S. Package Insert; Keytruda® U.S. Package Insert). Based on data from study KEYNOTE-048 pembrolizumab was approved for the first line treatment of patients with SCCHN in combination with platinum and fluorouracil with metastastic or unresectable, recurrent disease. Additionally pembrolizumab is approved as a first line monotherapy in patients with metastastic or unresectable disease whose tumors express PD-L1. Nivolumab is also approved in the European Union for the treatment of SCCHN in adults progressing on or after platinum-based therapy (Opdivo Summary of Product Characteristics).

In the KEYNOTE-012 (Mehra et al 2018) and KEYNOTE-055 (Bauml et al 2017) studies of pembrolizumab, participants with recurrent or metastatic SCCHN or platinum- and cetuximab-refractory SCCHN, respectively, had an ORR of 16%–18%.

A Phase III trial (CheckMate 141; Ferris et al 2018) demonstrated that participants who have platinum-refractory, recurrent, or metastatic SCCHN treated with nivolumab had a longer OS (median 7.7 vs. 5.1 months; HR 0.68; 95% CI: 0.54–0.86) and increased ORR (13.3% vs. 5.8%) than participants treated with single-agent investigator's choice of therapy.

Based on results of these clinical studies, blockade of the PD-1/PD-L1 pathway with atezolizumab, pembrolizumab, or nivolumab has demonstrated efficacy in participants with SCCHN.

Esophageal Squamous Cell Carcinoma

Clinical trials of PD-1 monoclonal antibodies have reported preliminary evidence of activity in a subset of participants with this disease. In the KEYNOTE-028 trial (NCT02054806), which was limited to participants with PD-L1-positive tumors, the esophageal cancer cohort showed objective responses after pembrolizumab therapy in 5 of 18 participants with SCC (28%) (Doi et al 2017).

A separate Phase II trial of nivolumab, which was conducted in Japan, in a SCC cohort, not-preselected for PD-L1 status, reported objective response in 11 of 64 participants (17.2%), including one complete responder (Kojima et al. 2016). Successor studies are now underway, including two trials evaluating pembrolizumab in the second- and third-line settings for advanced disease (NCT02564263 [KEYNOTE-181], NCT02559687 [KEYNOTE 180]) and nivolumab (NCT02569242).

While these immune CPIs certainly hold considerable promise, it seems to be apparent that only a subset of participants derived benefit from this class of agents (Wang et al 2016).

A therapeutic strategy of potentiating the effects of PD-1 antibodies by combining them with additional agents, in particular other immunotherapies, has already been demonstrated in certain solid tumors, but has not been looked at extensively in esophageal cancer. Results from a Phase I/II study of participants with esophageal, gastric, and gastroesophageal junction adenocarcinomas unselected for PD-L1 expression (CheckMate 032) treated with the combination of nivolumab alone or in combination with the anti-CTLA-4 antibody ipilimumab at prespecified dose levels showed a response rate of between 8-24% depending on the combination (Janjigian et al. 2018); these results have prompted plans to test the combination for this same patient population in Phase III study design.

Thus, other novel agents, such as *simlukafusp alfa*, are worth exploring further in esophageal cancer.

Cervical Squamous Cell Carcinoma

If cervical cancer disease persists or recurs after platinum-based chemoradiotherapy, options are limited and the prognosis is poor. Median OS with chemotherapy alone is typically around 13 months (Tewari et al. 2014).

In this latter setting, recently, bevacizumab, an antiangiogenic monoclonal antibody targeting vascularendothelial growth factor (VEGF), has been shown to improve median OS by 3.7 months in combination with chemotherapy as compared with chemotherapy alone. No standard treatments exist beyond this treatment regimen (Tewari et al. 2014).

Data from Phase Ib KEYNOTE-028 trial which included an expansion cohort of participants with advanced cervical SCC have shown an ORR of 17%, including 4 patients with a PR and 3 with SD (mean duration of response, 5.4 months) and a median OS of 11 months. In summary, pembrolizumab showed antitumor activity in participants with PD-L1-positive recurrent or metastatic cervical SCC (Frenel et al. 2017). The clinical benefit of pembrolizumab in advanced cervical cancer *was* further investigated in the Phase II KEYNOTE-158 trial (ClinicalTrials.gov identifier: NCT02628067) which has shown similar initial results with ORR of 12.2% (95% CI, 6.5% to 20.4%), with three complete and nine partial responses and median OS of 9.4 months in the total population and 11 months in the PD-L1 positive tumor population (Chung et al. 2019). However, response to pembrolizumab alone remains low, explaining the current evaluation of drug combinations with pembrolizumab *(NCT03786081)*.

Further approaches are the combination of two different types of immunotherapies *in the 2L/2L+ metastatic setting in cervical cancer*. For example, durvalumab, an anti–PD-L1 antibody, *was* combined with tremelimumab, an anti–CTLA-4 antibody, in a Phase I study (ClinicalTrials.gov identifier: NCT01975831) *in a study investigating breast, ovarian, colorectal, renal cell and cervical cancers. Other examples are tiragolumab, an anti-TIGIT antibody, that is being combined with atezolizumab in a Phase II study (ClinicalTrials.gov identifier: NCT04300647) or balstilimab, an anti-PD-1 antibody, being combined with zalifrelimab, an anti-CTLA-4 antibody, in a Phase II study (ClinicalTrials.gov identifier: NCT03495882).* Consequently, the currently available results provide a compelling rationale to further assess the activity of the combination of atezolizumab and *simlukafusp alfa* in participants with the following:

- Cohorts G & K: CPI-naïve advanced and/or metastatic SCCHN
- Cohorts H & L: CPI-experienced advanced and/or metastatic SCCHN
- Cohorts I & M: Previously treated CPI-naïve squamous esophageal cancer
- Cohorts J & N: Metastatic, persistent, or recurrent squamous cervical cancer

4.3.2 Rationale for Control Group

Part I Cohorts A, B, C, and F and all Part III cohorts will be single-arm cohorts.

Participants in Cohort D will be randomized to either receive QW/Q2W or Q3W dosing for the combination of *simlukafusp alfa* with atezolizumab or single-agent chemotherapy (gemcitabine or vinorelbine for participants who experienced disease progression during or after platinum/gemcitabine doublet chemotherapy).

In the recent years, the approval of CPI in first and second line of therapy yielded a patient population with a specific treatment history (i.e., platinum combination, CPI, and docetaxel pre-treated population). There is no reliable benchmark for this emerging population to be used as valid comparison for the evaluation of the proposed combination therapy. Therefore, the Cohort D will enroll a control arm. This control arm will allow a robust evaluation of *simlukafusp alfa* + atezolizumab combination in terms of ORR but also will allow the interpretation of progression-free survival (PFS) which is more relevant than ORR in this heavily pretreated population (PFS is typically very dependent on selection bias). This study arm aims to compare tumor response to *simlukafusp alfa* in combination with atezolizumab to the best supportive care available for this participant group with advanced and/or metastatic NSCLC after at least one previous regimen of anticancer therapy, including CPI treatment in patients who have experienced progressive disease during or after docetaxel treatment.

The two chemotherapeutic agents permitted in this study, vinorelbine (oral capsules or intravenous [IV] infusion) or gemcitabine (IV infusion), are internationally recognized and recommended treatment options in locally advanced stage III and metastatic NSCLC) (Eberhardt et al. 2015, Reck et al. 2016).

The European Society for Medical Oncology (ESMO) Guidelines (Planchard et al 2018) recommend vinorelbine single-agent chemotherapy as an alternative treatment option in patients with metastatic NSCLC and a PS of 2 and beyond. The National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2017 recommend vinorelbine single-agent chemotherapy as second-line treatment in patients who have experienced disease progression either during or after first-line therapy.

ESMO Guidelines (Planchard et al. 2018) recommend gemcitabine single-agent chemotherapy as an alternative treatment option in patients with metastatic NSCLC and a PS of 2 and beyond. The NCCN Guidelines Version 3.2017 recommend gemcitabine as monotherapy after progression on doublet chemotherapy or bevacizumab plus chemotherapy in patients with PS 0-2, and as maintenance therapy in PS of 2 patients following response to chemotherapy or SD.

4.3.3 Rationale for Open-Label Study

An open-label study design was chosen for this study for the following reasons. Given the known toxicities associated with single agent chemotherapy and due to different

dosing schedules, participants assigned to chemotherapy, as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo, which would pose a significant burden to participants. Adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing activity assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules. Activity analyses will only be performed at the pre-specified analysis timepoints in the protocol. Adequate steps also include a blinded review of the tumor scans and response assessments by an independent review as sensitivity analysis of the primary endpoint (see Section 9).

4.3.4 Rationale for Biomarker Assessments

Simlukafusp alfa was designed to preferentially activate immune cells in tumors with high FAP expression in the stroma. Extended peripheral activation and expansion of immune cells is expected due to the clearance of *simlukafusp alfa* being lower than that of non-conjugated cytokines. The specimens will be used for research purposes to identify biomarkers useful for predicting and monitoring response to the study treatment and safety; assessing the PD effects of the study treatment; and investigating the mechanism of therapy resistance. Additional markers may be measured in case a strong scientific rationale develops (see Section 8.8).

For participants with SCC (Part III only), information on the participant's status for Epstein-Barr virus (EBV) and high-risk HPV in tumor tissue will be collected and reported within 6 months of enrollment. This information will be extracted from the participant's record (if available) and may be confirmed centrally. Results are not utilized to determine eligibility for this study and participants can be enrolled irrespective of EBV/HPV status information.

4.3.4.1 Peripheral Blood Sample for Immunophenotyping

To assess the effect of the study treatment in the periphery, changes in T-cell and NK cell populations, and T-cell differentiation and proliferation as well as regulatory T cell numbers will be analyzed by FACS.

4.3.4.2 Tumor Biopsy Sample

Immune infiltration at diagnosis has been described as an emerging prognostic marker in several malignancies (Becht et al. 2016; Fridman et al. 2012). To investigate the possible impact of immune-cell density on PD effect, or clinical activity, of *simlukafusp alfa* in combination with atezolizumab, the immune cell density, such as CD8+ T and NK cells' expansion and infiltration, the change in PD-L1 levels in tumor microenvironment, and the expression of activation and proliferation markers (e.g., Ki67), will be determined in baseline, on-treatment and progression tumor biopsies. Emerging potentially-predictive markers of activity of immunotherapies, such as PD-1 expression, may also be investigated.

Biomarkers that may predict response versus resistance to study treatment will be explored in tumor tissue. Higher levels of CD8+, TEM, NK cell numbers, interferon gamma (IFN-γ), and PD-L1 have been associated with better clinical benefit from cancer immunotherapy treatment. Accordingly, the levels of these biomarkers will be investigated in this study population using IHC or gene expression analysis.

4.3.4.3 Plasma/Serum Samples

Soluble CD25, which has been described as a circulating marker of IL-2-mediated immune cell activation (Ribas et al. 2009), will be measured. Soluble FAP may be a prognostic marker in cancers with high stroma content (Javidroozi et al. 2012), and may be used to track disease burden. Administration of therapeutic antibodies can be associated with IRRs and cytokine release. Therefore, cytokines, including but not limited to IL-6, IFN-γ, tumor necrosis factor alpha (TNF-α), and inflammation markers, may be assessed in serum or plasma samples during treatment and in the event of an IRR.

HPV not only causes nearly all cases of cervical cancer (Schiffman et al. 1993), but also has a role in other indications, including SCCHN. HPV has been shown to have prognostic value in SCCHN with HPV+ patients showing improved response and survival compared to HPV- (Wang et al. 2015). Per the 8th edition of the American Joint Committee on Cancer (AJCC) in 2018, the tumor-node-metastasis (TNM) classification was updated to reflect that HPV+ and HPV– SCCHN cancers comprise two clinically different diseases (Denaro et al. 2018). It has been shown that the risk of developing nasopharyngeal carcinoma (NPC) is increased in patients who have serologic markers of EBV (Chien et al. 2001). Recent studies have demonstrated that EBV reactivation is involved in the carcinogenic process (Wu et al. 2018). Furthermore, it has been shown that the tumor microenvironment is different between EBV+ and EBV– NPC, with EBV+ tumors showing higher CD68 and FOX3 counts (Ooft et al. 2018). Therefore, HPV and EBV status may be examined in participants in Part III to better understand the correlation between virus infection and outcome of disease.

4.3.4.4 Whole Blood Sample for DNA Analysis

The killer cell immunoglobulin-like receptor (KIR)-human leukocyte antigen (HLA) mismatch was associated with response to immunocytokine treatment in a small participant cohort (Delgado et al. 2010). To investigate this potential association, or other genetic associations, a blood sample will be collected for determining KIR-HLA and, possibly, other immune genotypes.

Whole genome sequencing may be performed to investigate biomarkers that might predispose the participant for treatment associated autoimmunity or to a positive tumor response to the study treatment combination. This is in line with the European Medicines Agency Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products (Committee for Medicinal Products for Human [CHMP] 2015).

4.4 RATIONALE FOR DOSE AND TREATMENT SCHEDULE

4.4.1 *Simlukafusp Alfa*

The *simlukafusp alfa* dose and schedule have been selected on the basis of several factors.

The QW/Q2W schedule has been selected in an attempt to optimize tumor uptake of *simlukafusp alfa* and maximize pharmacodynamic effects during Cycle 1. Those effects are then sought to be maintained at a new steady state with the Q2W dosing from Cycle 3 onwards. A population PK/PD was developed based on clinical data collected so far. *Simlukafusp alfa* PK behavior is being described with a target-mediated drug disposition (TMDD) model with expansion of the target (interleukin-2 receptor [IL-2R]) that explains the reduced exposure following multiple dosing. The expansion of the target pool is in line with the mechanism of action of *simlukafusp alfa* and is also supported by observations of immune cell counts (expressing the IL2R target), which expand in response to treatment. The expansion of IL-2R positive cells during Cycle 1 requires the up-titration of the dose from 15 to 20 mg in order to limit the reduction of drug exposure. Without up-titration, drug exposure would decline on average by approximately 40% to 50% when the drug is administered weekly. Following the intense schedule (QW), on Cycle 3 and onwards, a relaxed schedule (Q2W) has been selected based on *simlukafusp alfa* safety, tolerability, and hypothesized pharmacodynamic changes. The relaxed schedule is designed to provide constant *simlukafusp alfa* exposure to the tumor microenvironment, which is hypothesized to continuously drive tumor infiltrating immune cell expansion. This enforced expansion might be required for clinical activity in tumors with sparse immune cell infiltration.

The Q3W treatment schedule of this study consists of an every 3-week administration of *simlukafusp alfa* and atezolizumab. The hypothetical mechanism of action tested with this dosing regimen investigates the benefit of stimulating tumor-infiltrating immune cells only periodically with *simlukafusp alfa* and allows relaxation of PD effects between administrations. This pulsatile exposure might be sufficient to drive T-cell proliferation in tumors with brisk immune-cell infiltration. With a Q3W administration, *simlukafusp alfa* will be eliminated from the peripheral circulation prior to the next *simlukafusp alfa* administration. In addition, the number of IL-2R expressing cells in the periphery will return to their baseline levels prior to the next *simlukafusp alfa* administration. It is, therefore, predicted that no up-titration will be required for this dosing regimen.

Both differentiated *simlukafusp alfa* exposure concepts warrant clinical exploration in order to determine the most active schedule for further development. In cohorts where both schedules are explored, participants are assigned to one schedule by randomization. In cohorts enrolling CPI-experienced participants, the expected activity signal is difficult to interpret, because there is no experience on how active another CPI can be in that setting when combined with an immune modulator. Therefore, a control arm may be introduced. Those participants receive established conventional

chemotherapy, which allows the calibration of the obtained activity signal from RO6874821 in combination with atezolizumab.

Other factors considered in the selection of the *simlukafusp alfa* dose and schedule, include the following:

1. Clinical experience from *simlukafusp alfa* administered as single agent

   simlukafusp alfa as a single agent is currently being investigated in the ongoing BP29842 Phase I study. At the time of clinical cutoff date of 11 March 2019, a total of 57 participants, 53 evaluable patients, had received multiple-ascending doses of *simlukafusp alfa* intravenously up to 35 mg in a once weekly (QW) schedule. The MTD has been declared at the 15 mg, followed by an up-titration to 20 mg at the second *simlukafusp alfa* administration in a QW schedule. Based on the collected data, the predicted toxicity, measured in terms of probability of DLT, at the current proposed starting dose lies within the acceptable range of 20% to 30%.

   Analyzing the *simlukafusp alfa* PK data at doses from 5 to 25 mg QW, it was observed that exposure (area under the concentration–curve; AUC) increased with dosage as well as maximum concentration (C_{max}) after the first administration. However, after multiple administrations, exposure was reduced, an effect considered to be mediated via a self-induced clearance mechanism. Similar behavior was observed with cergutuzumab amunaleukin. To compensate for this reduction in exposure, it is proposed to up-titrate the dose at the second *simlukafusp alfa* administration, where a substantial reduction in exposure of approximately 40% to 50% is observed. The *simlukafusp alfa* up-titrated dose on the second administration was identified on the basis of model-based approaches which aim to predict a higher dosage to compensate for the TMDD effect and maintain a dose equivalent exposure.

   After the starting dose of 15 mg, the model predicted dose for the second administration is 20 mg. The participants have been dosed up to 25 mg for the first dose and up to 35 mg for subsequent doses. No DLT has been observed with the starting dose of 15 mg. In participants receiving 20 mg (as the first or subsequent dose), liver function abnormalities, and fatigue have been reported. Those AEs were manageable and resolved.

2. Clinical experience with cergutuzumab amunaleukin

   Cergutuzumab amunaleukin is being tested in combination with atezolizumab (Study BP29435). Dosage escalation has been completed, and cergutuzumab amunaleukin was explored up to 20 mg Q2W and with up-titration at doses up to 20/25 mg in combination with atezolizumab 800 mg Q2W, and up to 15-20 mg QW in combination with atezolizumab 1200 mg Q3W. At the time of clinical cutoff date of 8 April 2019, a total of 75 participants had received cergutuzumab amunaleukin in

the above regimen. Overall, the safety profile is considered acceptable and consistent with those of IL-2 and atezolizumab therapies.

3. Part I Only: Clinical experience *simlukafusp alfa* administered in combination with atezolizumab in participants with 2/3L NSCLC.

   As of the clinical cutoff date of 11 March 2019, preliminary safety data were available for 63 participants who have failed ≥1 line of therapy dosed with combination treatments in Study BP40234, Part I. Participants received either 10 or 15 mg Cycle 1 Day 1 dose of 15 mg *simlukafusp alfa* in combination with 840 mg atezolizumab (Q2W) or 1200 mg Q3W. The current dose administration is 10 mg flat dose of *simlukafusp alfa*.

   In participants treated in Cohort A (CPI naïve), eight AEs were reported: pyrexia, chills, headache, arthralgia, AST increased, ALT increased, bilirubin increased, and nausea. All of these AEs were considered to be related to study treatment. Most AEs were mild or moderate (Grade 1 or 2) in intensity; the AST/ALT increased AEs were of Grade 3 severity.

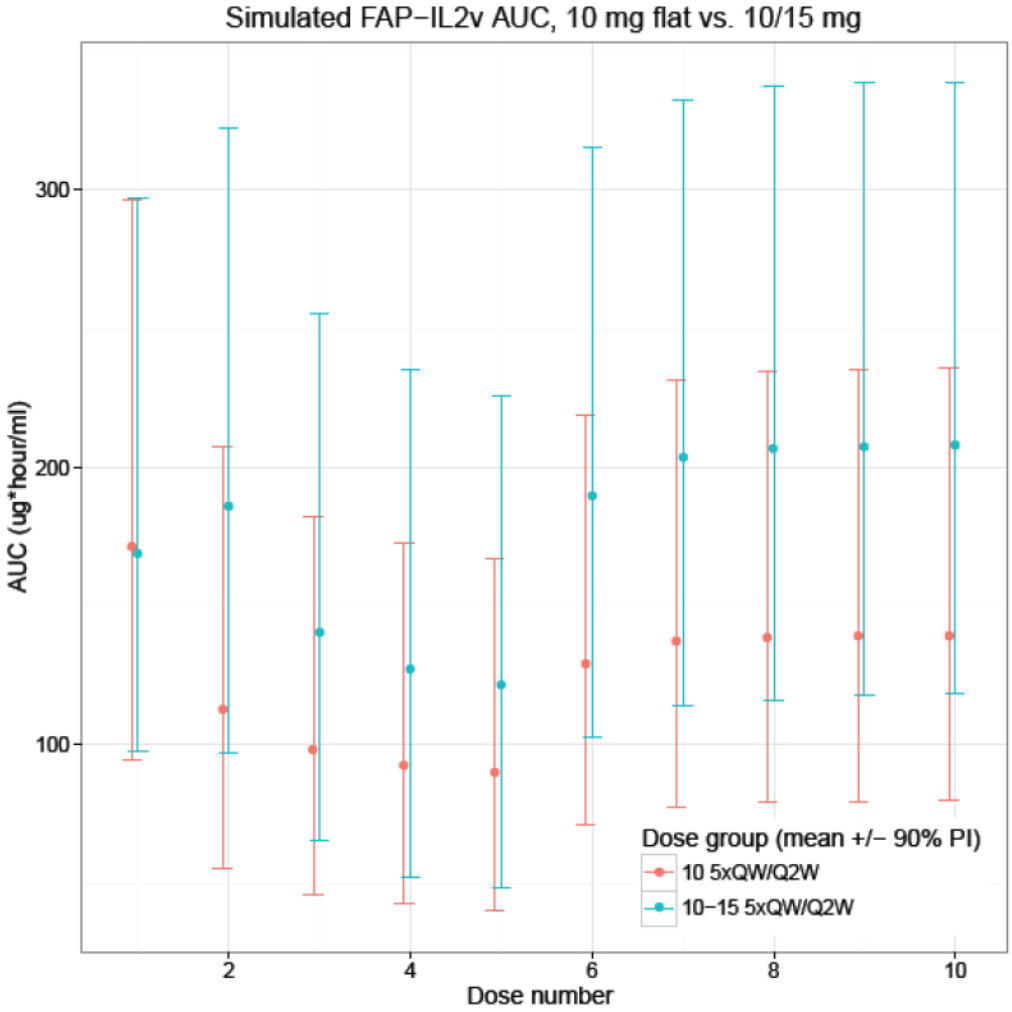
   In Cohort B (CPI experienced), 33 AEs were reported in the four participants. Pyrexia, AST increased, ALT increased, and rash were the most commonly reported AEs in this arm. Of the 33 AEs reported, 27 were considered to be related to study treatment (n=4; 100%). Most AEs were mild or moderate (Grade 1 or 2) in intensity. Three AEs of severity Grade 4 were reported: lymphocyte count decreased (n=1; related to study treatment) and hypokalemia and hypophosphatemia (n=1; not related to study treatment). One event of bronchoaspiration with fatal outcome, which was not considered to be related to study treatment, was reported in one participant.

   In Cohort A, no serious AEs (SAEs) have been reported.

   In Cohort B, six SAEs have been reported in three participants (75.0%): one pyrexia, one transaminitis, one rash acneiform, one hypotension, one respiratory infection, and one bronchoaspiration. Four SAEs, pyrexia, transaminitis, respiratory infection, and rash acneiform, were considered to be related to study treatment.

In an effort to improve the treatment tolerability, based on the data above, a dose adjustment by 5 mg resulting in the following doses of 10 mg on Cycle 1 Day 1 followed by 15 mg on Cycle 1 Day 8 or a flat dose schedule at 10 mg is to be explored. Based on a simulation using the population PK model, the 10-mg flat dose regimen shows overlapping exposures to the dosing regimens of 10 mg followed by 15 mg, as shown in Figure 4.

Figure 4 Pharmacokinetic Model of 10-mg Flat or 10-15 mg Dose Regimen



Abbreviations: AUC = area under the concentration–time curve; FAP-IL2v = *simlukafusp alfa*; QW = once weekly; Q2W = every 2 weeks.

The selected dosing scheme may be modified. Please see Section 6.6.1 for further details.

4.4.2 Atezolizumab

Atezolizumab is approved for locally advanced or metastatic urothelial carcinoma and for metastatic NSCLC as a 30-minute IV infusion Q3W at the dosage of 1200 mg with a first administration as a 60-minute IV infusion (Tecentriq® US Package Insert). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Data suggest that the 15-mg/kg atezolizumab Q3W regimen (equivalent to a fixed dosage of 840 mg Q2W) would be sufficient to both maintain concentrations higher than minimum concentration (C_{trough}), and further safeguard against both inter-participant variability and potential effect of anti-drug antibodies (ADAs) that could lead to

subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab Q3W regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab Q3W regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab Q3W level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure after a fixed dosage, or dosage adjusted for weight. On the basis of this analysis, a fixed flat dosage of 840 mg Q2W, or 1200 mg Q3W, has been selected (equivalent to a body weight−based dosage of 15 mg/kg Q3W).

Further details are provided in the Atezolizumab Investigator's Brochure.

4.5 END OF STUDY DEFINITION

The end of the study is defined as the last participant's last visit (LPLV) per protocol (includes the follow-up visits at 28 days and 3 months after the last dose of any study drug, and 120 days after the last dose of atezolizumab, whichever occurs last) or the date at which the last data point from the last participant required for statistical analysis is received (Last Participant, Last Observation), whichever is the latest date (see also Section 7.1).

5. STUDY POPULATION

The study population rationale is provided in Section 4.3.1.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

5.1.1 General Inclusion Criteria for all Participants

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Signed informed consent.

Age

2. Age ≥ 18 years

Type of Participants and Disease Characteristics

3. Measurable disease, as defined by RECIST v1.1
4. ECOG Performance Status 0 or 1 or KPS ≥ 70
5. Life expectancy of ≥ 12 weeks

6. Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system [CNS] metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
7. Confirmed at least one tumor lesion with location accessible to safely biopsy per clinical judgment of the treating physician and the participant's consented willingness to undergo baseline and on-treatment tumor biopsies for PD biomarker analysis *(not applicable to Part I Cohort A)*:

   Previously irradiated lesions should not be counted as target lesions.

   Lesions that are intended to be biopsied should not be counted as target lesions.

   Note: Biopsies are not applicable to participants in Cohorts G, H, K, and L presenting with a single target lesion and absence of any non-target lesion.

   Other exceptions may apply and require discussion and agreement between the Investigator and the Sponsor.
8. Consent to provide an archival tumor tissue sample
9. Adequate cardiovascular function:

   New York Heart Association (NYHA) Heart Failure Stage ≤ 2

   a. Left ventricular ejection fraction $\geq 50\%$, as determined by multiple-gated acquisition scan (MUGA) or transthoracic echocardiogram (TTE)
   b. Baseline-corrected QT (QTcF) interval ≤ 470 milliseconds
   c. Resting systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 100 mmHg (average of ≥ 3 readings on ≥ 2 sessions)
   d. Resting heart rate between 45 to 100 bpm
10. Adverse events related to any previous radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade ≤ 1, except alopecia (any grade) and Grade 2 peripheral neuropathy
11. Adequate hematological function: neutrophil count of $\geq 1.5 \times 10^9$ cells/L, platelet count of $\geq$ 100,000/L, hemoglobin $\geq$ 9 g/dL (5.6 mmol/L), lymphocytes $\geq 0.5 \times 10^9$ cells/L

    Borderline lymphocyte cell counts may be confirmed by a manual count.
12. Adequate liver function, including total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; direct bilirubin $\leq$ ULN for participants with total bilirubin levels $> 1.5 \times$ ULN), AST, and ALT $\leq 2.5 \times$ ULN.

    In case of liver metastases AST and ALT: $\leq 5 \times$ ULN). Eligibility of patients with liver metastases should be discussed and agreed with the Sponsor if AST, ALT are between 2.5 $\times$ and 5 $\times$ ULN.

13. Adequate renal function: serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance by Cockcroft-Gault formula (see Appendix 6) ≥ 50 mL/min for participants in whom, in the Investigator's judgment, serum creatinine levels do not adequately reflect renal function
14. Participants with unilateral pleural effusion (indications other than NSCLC) are eligible if they fulfill both of the following:
    a. NYHA Class 1
    b. Forced expiratory volume 1 (FEV1) and forced vital capacity (FVC) >70% of predicted value; participants with lung metastases should present with DLCO >60% of predicted value

Sex

15. Male and female participants

    The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

a. Female participants
A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5).

OR

- A WOCBP, who:
  - Agrees to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 4 months after the last dose of study drug for *simlukafusp alfa* and for at least 5 months after the last dose of atezolizumab

    Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, and hormone-releasing intrauterine devices (see Appendix 5).
  - Have a negative pregnancy test (serum) within the 7 days before the first study treatment administration

b. Male participants
   - During the treatment period and for at least 2 months after the last dose of *simlukafusp alfa*, agreement to the following:
     - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with partners who are WOCBP (as defined in Section 1 of Appendix 5)
     - With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo
     - Refrain from donating sperm

5.1.2 Specific Inclusion Criteria for Participants in Part I

16. Advanced or metastatic NSCLC patients who have failed at least one previous regimen of anticancer therapy
17. Tumors with a known sensitizing mutation (e.g., EGFR, ALK, ROS rearrangement, BRAF V600E mutation) must have experienced disease progression (during or after treatment) or intolerance to treatment with all available standard−of-care (SOC) targeted therapies, respectively

5.1.2.1 Cohort A: Checkpoint Inhibitor Naïve NSCLC Participants

18. Participants must have progressed on at least one previous systemic therapy for advanced or metastatic NSCLC disease

5.1.2.2 Cohort B: Checkpoint Inhibitor Experienced NSCLC Participants

19. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

5.1.2.3 Cohort C: Checkpoint Inhibitor Naïve Participants

20. Participants must have progressed on at least one previous systemic therapy for advanced or metastatic NSCLC disease
21. Participants must have accessible tumor lesions that can be safely biopsied

5.1.2.4 Cohort D: Checkpoint Inhibitor Experienced Participants

22. Participants who experienced disease progression during or following treatment with a platinum-containing regimen and a CPI, given in combination as one line of therapy or as two separate lines of therapy

    Participants should have experienced disease progression on docetaxel therapy.

23. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

5.1.2.5 Cohort F: Checkpoint-Inhibitor Experienced, Platinum Experienced, Docetaxel-Naïve NSCLC Participants

24. Participants who experienced disease progression during or following treatment with a platinum-containing regimen and a CPI, given in combination as one line of therapy or as two separate lines of therapy
25. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved)

    The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

    Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

5.1.3 Specific Inclusion Criteria for Participants in Part II

26. Previously untreated NSCLC without sensitizing mutation with available targeted therapy as standard-of-care (SoC)

5.1.3.1 Cohort E: Participants with High-Tumor PD-L1 Expression

27. Participants with a PD-L1 TPS $\geq$ 50%, who have not received any prior systemic therapy for metastatic NSCLC

5.1.4 Specific Inclusion Criteria for Participants in Part III

28. Participant must have accessible tumor lesions that can be safely biopsied

    Biopsies are not applicable to participants in Cohorts G, H, K, and L presenting with a single target lesion and absence of any non-target lesion.

5.1.4.1 Cohorts G & K: CPI-Naïve SCCHN Participants

29. Confirmed diagnosis of recurrent or metastatic SCCHN

5.1.4.2 Cohorts H & L: CPI-Experienced SCCHN Participants

30. Confirmed diagnosis of recurrent or metastatic SCCHN
31. Prior CPI-containing treatment for recurrent or metastatic disease.
32. Experienced progression or intolerance while receiving $\leq$ 2 line(s) of standard therapy
33. Participants must have experienced documented disease progression on or after CPI therapy (investigational or approved).

The CPI may have been administered as monotherapy or as part of a combination regimen at any time during the anti-cancer treatment before study enrollment.

Participants with suspected or documented disease progression within the first 12 weeks of CPI therapy may not be eligible and require discussion with the Sponsor. Screening tumor assessment should confirm previous progression.

5.1.4.3 Cohorts I & M: Esophageal Squamous Cell Carcinoma

34. Confirmed diagnosis of recurrent or metastatic esophageal cancer
35. Experienced progression or intolerance while receiving ≥1 line of standard therapy

5.1.4.4 Cohorts J & N: Cervical Squamous Cell Carcinoma

36. Confirmed diagnosis of metastatic, persistent, or recurrent squamous cervical cancer
37. Experienced progression or intolerance while receiving ≥1 line of standard therapy

5.2 EXCLUSION CRITERIA

5.2.1 General Exclusion Criteria for all Participants

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Symptomatic or untreated CNS metastases.
2. History of treated asymptomatic CNS metastases with any of the following criteria:
   a. Metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
   b. History of intracranial hemorrhage or spinal cord hemorrhage
   c. Lacking radiographic demonstration of improvement upon the completion of CNS-directed therapy and evidence of interim progression between the completion of CNS-directed therapy and the baseline radiographic study
   d. Ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dosage are allowed
   e. Stereotactic radiation or whole-brain radiation within 28 days before study treatment administration
   f. Last CNS radiographic study <4 weeks since completion of radiotherapy and <2 weeks since discontinuation of corticosteroids
   g. CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days before study treatment administration
3. 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 before enrollment

4. Leptomeningeal disease
5. An active second malignancy (exceptions are non-melanoma skin cancer, cervical carcinoma in situ, or prostate carcinoma that is in remission under androgen deprivation-therapy for >2 years, or participants who have a history of malignancy and have been treated with curative intent and the participant is expected to be cured as per Investigator's assessment)

   Other exceptions may apply and require discussion between the Investigator and the Sponsor.
6. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, and known autoimmune diseases or other disease with ongoing fibrosis (such as, scleroderma, pulmonary fibrosis, and emphysema)
7. Episode of significant cardiovascular/cerebrovascular acute disease within 6 months before study treatment administration, including any of the following: hypertensive crisis/encephalopathy, uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), unstable angina, transient ischemic attack/stroke, congestive heart failure of any NYHA classification (for NYHA classification, refer to inclusion criteria), serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia), history of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism), hypertensive encephalopathy
8. Active or uncontrolled infections
9. Known HIV infection
10. Active hepatitis A (HAV) hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D (HDV) or hepatitis E (HEV) infection
11. Severe infection within 4 weeks before study treatment administration including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
12. History of chronic liver disease or evidence of hepatic cirrhosis
13. Dementia or altered mental status that would prohibit informed consent
14. History of active or suspicion of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

    Participants with a history of autoimmune hypothyroidism on a stable dosage of thyroid replacement hormone may be eligible with approval by the Medical Monitor.

    Participants with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study with approval by the Medical Monitor.

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

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

16. Bilateral pleural effusion confirmed by x-ray
17. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug
18. Concurrent therapy with any other investigational drug (defined as a treatment for which there is currently no regulatory authority-approved indication)
19. Immunomodulating agents:
    a. Last dose with any of the following agents, for example, etanercept, infliximab, tacrolimus, cyclosporine, mycophenolic acid, alefacept, or efalizumab (or similar agents) $<$28 days before study treatment administration.
    b. Previous immunotherapies including, but not limited to, any cytokine therapies, particularly IL-2 and IL-2 conjugates, interferon alpha (IFN-α), interferon beta (IFN-β)
    c. Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease)
20. Treatment with systemic immunosuppressive medications including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents within 2 weeks prior to Cycle 1 Day 1

    Participants who have received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of $\leq$10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

21. Last dose with any cytostatic treatments $<$ 28 days before study treatment administration
22. Radiotherapy within the last 4 weeks before start of study treatment administration, with the exception of limited field palliative radiotherapy.
23. Administration of a live, attenuated vaccine within 4 weeks before Cycle 1 Day 1.

Other Exclusions

24. Major surgery or significant traumatic injury $<$28 days before study treatment administration (excluding fine needle biopsies) or if wound healing has not completed after surgery or anticipation of the need for major surgery during study treatment
25. Known hypersensitivity to any of the components of the *simlukafusp alfa* drug product or atezolizumab drug product, including but not limited to hypersensitivity to

Chinese Hamster Ovary cell products or other recombinant human or humanized antibodies

26. Severe dyspnea at rest or requiring supplementary oxygen therapy

Eligibility of participants who require blood transfusion before and after the start of the study treatment should be discussed by the Sponsor and Investigator.

5.2.2 Specific Exclusion Criteria for Participants in Part I

27. Participants with pleural effusion (unilateral or bilateral) confirmed at screening by x-ray

5.2.2.1 Cohort A and C: Checkpoint Inhibitor Naïve NSCLC Participants

28. Previous CPI therapy (e.g., anti–CTLA-4, anti–PD-1/L1) before study enrollment

5.2.2.2 Cohort B: Checkpoint Inhibitor Experienced NSCLC Participants

29. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
30. Any history of an immune-related Grade ≥3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

5.2.2.3 Cohort D: Checkpoint Inhibitor Experienced NSCLC Participants

31. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
32. Any history of an immune-related Grade ≥ 3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)
33. Known sensitivity and contraindications to the comparative chemotherapy agent gemcitabine or vinorelbine

5.2.2.4 Cohort F: Checkpoint Inhibitor Experienced, Platinum Experienced, Docetaxel Naïve NSCLC Participants

34. Participants treated with other non-platinum based chemotherapy treatment
35. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
36. Any history of an immune-related Grade ≥3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

5.2.3 Specific Exclusion Criteria for Participants in Part II

37. Participants with pleural effusion (unilateral or bilateral) confirmed at screening by x-ray

5.2.4 Specific Exclusion Criteria for Participants in Part III

38. Locally curative options are available for participant's disease

5.2.4.1 Cohorts G, I, J, K, M, & N: CPI-Naïve SCC Participants

39. Participants must not have received CPI therapy (e.g., anti CTLA-4, anti PD-1/L1) before study enrollment

5.2.4.2 Cohorts H & L: CPI-Experienced SCCHN Participants

40. Participants who discontinued CPI therapy for CPI-associated toxicity or intolerability
41. Any history of an immune-related Grade $\geq$3 AE attributed to previous cancer immunotherapy (with the exception of endocrinopathy managed with replacement therapy)

5.3 LIFESTYLE CONSIDERATIONS

Participants will be expected to follow protocol requirements for contraception (see Appendix 5) and study center rules during visits, but there are no other lifestyle restrictions during the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

Re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized with the 28-day screening window due to a study halt, logistical, personal or technical reasons. In order to re-screen such a participant, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days before randomization. If a baseline biopsy sample was taken, this does not need to be repeated unless the period is more than 56 days from the sample to the Cycle 1 Day 1 visit, and the participant received no other cancer therapy since the baseline biopsy.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a temporary condition (e.g., active infection) may be re-screened after agreement with the Sponsor.

In case of uncertain or questionable results, any of the tests performed during screening may be repeated before study treatment administration to confirm eligibility (or clinical significance).

5.5 RECRUITMENT PROCEDURES

Participants may be identified for potential recruitment using pre-screening enrollment logs, independent ethics committee (EC)/institutional review board (IRB)-approved

newspaper/radio advertisements, and mailing lists, before consenting to take part in this study.

An Interactive Response Technology (IRT) system will be utilized to manage (pre-) screening, randomization (Cohort D and E) and enrollment (all other cohorts). All pre-screening evaluations must be recorded in the IRT system with a proposed cohort. Roche will review and approve the pre-screened participants for the proposed cohort. After signing informed consent, the screening transaction should be performed in the IRT system and once it is confirmed that participants meet all eligibility criteria the participants should be enrolled or randomized in the respective cohort using the IRT system.

Rescreening is allowed if the criteria described in Section 5.4 are met. Rescreening is only allowed once. Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purpose of the study, *simlukafusp alfa*, atezolizumab, gemcitabine (IV), and vinorelbine (oral and IV) are considered investigational medicinal products (IMPs). All IMPs required for completion of this study (*simlukafusp alfa*, atezolizumab, gemcitabine IV, and vinorelbine oral and IV) will be provided as study medication by Roche or its designee in compliance with local drug management regulations. For information on the formulation, packaging, and handling of vinorelbine (oral and IV) and gemcitabine (IV), see the local Prescribing Information for each drug and formulation (vinorelbine).

All study treatment administration will be at the study center under supervision of site staff.

6.1 TREATMENTS ADMINISTERED

Study treatments must be administered in a clinic or hospital equipped for systemic (IV) cancer treatment. Full emergency resuscitation facilities should be immediately available, and participants should be under close observation by the Investigator at all times. In case of infusion-associated AEs in participants, the signs and symptoms should have fully resolved before the participant is discharged.

In all participants, atezolizumab will be administered first over 60 (±15) minutes. The participant should be observed for at least 2 hours after the first administration of atezolizumab before receiving *simlukafusp alfa*. For subsequent administrations of atezolizumab, the participant should be observed for at least 1 hour before receiving

simlukafusp alfa, and must have recovered from any acute toxicity mediated by the preceding administration of atezolizumab. *Simlukafusp alfa* will then be administered by IV infusion over a minimum of 2 hours (120 min). If the first infusion is well-tolerated as defined by an absence of Grade ≥2 IRRs, the subsequent infusion may be given over 0.5 hours (30 min). If the 30-minute infusion is well-tolerated, all subsequent infusions may be delivered over 30 minutes.

Table 10 summarizes the treatments administered.

Table 10 Summary of Treatments Administered

Study Treatment Name:	*Simlukafusp Alfa*	Atezolizumab
Dosage Formulation:	Solution	Solution
Unit Dose Strength(s)/Dosage Level(s):	25 mg/mL	60 mg/mL
Dose:	Part I: QW/Q2W schedule: 10-mg flat dose [a] Q3W schedule: 10-mg flat dose Part II: QW/Q2W schedule: 10-mg flat dose [a] Q3W schedule: 10-mg flat dose Part III: QW/Q2W schedule: 10-mg flat dose Q3W schedule: 10-mg flat dose	Q2W schedule: 840 mg Q3W schedule: 1200 mg
Route of Administration:	IV infusion	IV infusion
Dosing Regimen	QW/Q2W schedule: weekly for the first 4 weeks followed by every 2 weeks Q3W schedule: every 3 weeks	QW/Q2W schedule: every 2 weeks Q3W schedule: every 3 weeks
Packaging and Labeling:	*Simlukafusp alfa* will be provided as a sterile, colorless to slightly brownish solution for infusion in single-dose 2-mL glass vials. Each vial contains *simlukafusp alfa* at a concentration of 25 mg/mL. For further information please refer to the *Simlukafusp alfa Investigator's Brochure* and the Pharmacy Manual.	Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

IV = intravenous; QW = weekly; Q2W = every 2 weeks; Q3W = every 3 weeks.

[a] The previous versions of the protocol utilized a schedule with higher dose levels: 15mg on Cycle 1 Day 1 followed by 20 mg on Cycle 1 Day 8; 10 mg on Cycle 1 Day 1 followed by 15 mg on Cycle 1 Day 8; and 10-mg flat dose. However, the schedule was restricted to only the 10-mg flat dose in Version 6.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

Please see the *Simlukafusp alfa* and Atezolizumab Investigator's Brochures and Pharmacy Manuals for more details.

6.1.1 *Simlukafusp Alfa*

Simlukafusp alfa will be administered (after completion of atezolizumab administration) by IV infusion over a minimum of 2 hours (120 min). If the first infusion is well-tolerated as defined by an absence of Grade ≥2 IRRs, the subsequent infusion may be given over 0.5 hours (30 min). If the 30-minute infusion is well-tolerated, all subsequent infusions may be delivered over 30 minutes. If the dosage of *simlukafusp alfa* is up-titrated in a participant, the higher dose should also be administered over 2 hours in the first instance, as above. Participants must be monitored for 2 hours after the first dose of *simlukafusp alfa*, and after the first dose of any subsequent up-titrations.

Premedication and monitoring of participants is described in Table 11.

6.1.2 Atezolizumab

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

Premedication and monitoring of participants are described in Table 12.

6.1.3 Gemcitabine

Gemcitabine, in combination with cisplatin, is indicated as first-line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine monotherapy can be considered in elderly patients or those with ECOG Performance Status 2.

Participants randomized to receive single-agent gemcitabine will receive chemotherapy per relevant local guidelines and Summary of Product Characteristics (SmPC) management. Doses and dose modifications for the selected single-agent chemotherapy should be made per relevant local guidelines and prescribing information.

Gemcitabine may be administered intravenously at 1000-1250 mg/m^2 on Days 1 and 8 every 21 days or on Days 1, 8, and 15 every 28 days.

Please refer to the local SmPC for gemcitabine for dosing information.

6.1.4 Vinorelbine

Vinorelbine is indicated as a single agent or in combination for the first-line treatment of stage III or IV NSCLC.

Participants randomized to receive single-agent vinorelbine will be treated (orally or intravenously) per relevant local guidelines and SmPC management. Reliable dose correspondence has been confirmed between vinorelbine 80 mg/m^2 oral and 30 mg/m^2 IV (Bourgeois et al. 2007).

Vinorelbine for infusion may be administered at 25-30 mg/m^2 on Days 1 and 8 every 21 days or on Days 1, 8, and 15 every 28 days.

Vinorelbine for oral administration may be administered at 60-80 mg/m^2 on Days 1 and 8 every 21 days or Days 1, 8, and 15 every 28 days, with weekly dosing recommended in some labels. Please refer to the local SmPC for vinorelbine for dosing information.

6.1.5 Additional Required Medication: Pre-medications

Any pre-medication doses administered should be in compliance with the respective SmPC. For further details, see the respective local Prescribing Information for chemotherapy agents.

All pre-medications should be captured as concomitant medications in the participant's eCRF.

6.1.5.1 Pre-Medication for Participants Receiving *Simlukafusp Alfa*

Mild-to-moderate presentations of systemic reactions that may present as influenza-like illness with symptoms such as fever, chills, fatigue, and myalgia are associated with *simlukafusp alfa* infusions. These symptoms may occur despite premedication and may be treated symptomatically with antipyretics, analgesics, and antihistamines as indicated. Premedication and monitoring of participants is described in Table 11.

Table 11 Administration of *Simlukafusp Alfa* Infusions

First Infusion	Subsequent Infusions
• Premedication with antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist), anti-pyretics (acetaminophen 500–1000 mg PO/IV or alternatively ibuprofen 400–600 mg or other NSAIDS per institutional standard if acetaminophen cannot be tolerated), an anti-emetic, and hydration with 500 mL crystalloid fluid is recommended [a] • After completion of study drug administration, acetaminophen 500 mg Q8H Days 1–3 (maximum 2000 mg per day) and ibuprofen 400 mg Q6H Days 1–3 (maximum 2400 mg per day) may be prescribed. After Day 3, acetaminophen and ibuprofen may be taken PRN	• Premedication with antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist), anti-pyretics (acetaminophen 500–1000 mg PO/IV or alternatively ibuprofen 400–600 mg or other NSAIDS per institutional standard if acetaminophen cannot be tolerated), an anti-emetic, and hydration with 500 mL crystalloid fluid is recommended.[a] • After completion of study drug administration, acetaminophen 500 mg Q8H Days 1–3 (maximum 2000 mg per day) and ibuprofen 400 mg Q6H Days 1–3 (maximum 2400 mg per day) may be prescribed. After Day 3, acetaminophen and ibuprofen may be taken PRN. • Vital signs (pulse rate, respiratory rate, blood pressure and temperature; pulse oximetry if clinically indicated) should be recorded prior to the infusion and at the end of the infusion at time points stated in Table 3 and Table 6 for the Q2W and Q3W schedules, respectively. Participants who experienced Grade 3 vital sign abnormalities during the previous infusion should be monitored at the site for at least 24 hours after the infusion.

Table 11 Administration of *Simlukafusp Alfa* Infusions (cont.)

• First Infusion	• Subsequent Infusions
• Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be recorded prior to the infusion • *Simlukafusp alfa* should be infused over 120 (± 5) minutes • Vital signs should be recorded at the end of the infusion and, if clinically indicated, during the infusion and the following day at time points stated in in Table 3 and Table 6 for the Q2W and Q3W schedules, respectively • Participants must be monitored, with the infusion line in place, for 2 hours after the infusion • Based on the participant's post-treatment condition, consider monitoring participants for an additional period of time after the infusion, as clinically indicated, and look for signs of pyrexia, rigors and hypotension. Keep the participant overnight if not responding to corrective measures or if otherwise clinically indicated.	• If the participant experienced a Grade 2 IRR [b] during the previous infusion, premedication with antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist), anti-pyretics (acetaminophen 500–1000 mg PO/IV or alternatively ibuprofen 400-600 mg or other NSAIDS per institutional standard if acetaminophen cannot be tolerated), an anti-emetic, and hydration with 500 mL crystalloid fluid must be administered approximately 30 minutes prior to the infusion.[a] • If the participant experienced a Grade 3 IRR[b] during the previous infusion, premedication with antihistamines (both an H1-receptor antagonist and an H2-receptor antagonist), anti-pyretics (acetaminophen 500–1000 mg PO/IV or alternatively ibuprofen 400–600 mg or other NSAIDS per institutional standard if acetaminophen cannot be tolerated), an anti-emetic, hydration with 500 mL crystalloid fluid, and hydrocortisone (200 mg IV or equivalent) must be administered approximately 30 minutes prior to the infusion.[a] • If the previous infusion was well tolerated (defined as absence of Grade 2 IRRs), *simlukafusp alfa* may be infused over 30 (± 5) minutes. If the previous infusion was not well tolerated, *simlukafusp alfa* should be infused over 120 (± 5) minutes. • If the previous infusion was well tolerated, the peripheral catheter should remain in place for 30 minutes from the end of infusion. If no infusion-related symptoms occur during the 30 minutes, the peripheral catheter may be removed. • Based on the participant's post-treatment condition, consider monitoring participants for an additional period of time after the infusion as clinically indicated and look for signs of pyrexia, rigors and hypotension. Keep the participant overnight if not responding to corrective measures or if otherwise clinically indicated.

D = Day; IRR = infusion-related reaction; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral; PRN = pro re nata, as needed.

[a] Premedication guidelines may change during the course of the study.

[b] *simlukafusp alfa* should be permanently discontinued for participants who experience a Grade 4 IRR.

For management of IRRs following *simlukafusp alfa* infusion, please refer to Section 8.3.8

6.1.5.2 Pre-Medication for Participants Receiving Atezolizumab

No pre-medication is indicated for the administration of Cycle 1 of atezolizumab. However, participants who experience an IRR with Cycle 1 of atezolizumab may receive pre-medication as listed in Table 12.

Table 12 Administration of First and Subsequent Atezolizumab Infusions

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

Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks and AE management guidelines for atezolizumab.

6.1.6 Gemcitabine and Vinorelbine

Please refer to the local SmPC for gemcitabine and vinorelbine for dosing information.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study medications *simlukafusp alfa* and atezolizumab will be provided by the Sponsor. Study medications gemcitabine (IV) and vinorelbine (oral or IV) will either be provided by the Sponsor where required by local health authority regulations or sourced locally with reimbursement by the Sponsor in compliance with local drug management regulations.

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

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

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

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals, and temperature conditions.
- Report any deviations or product complaints to the Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule (where applicable).

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the *Simlukafusp alfa* and Atezolizumab Investigator's Brochures or local prescribing information for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Part I Cohorts A, B, C, and F are open-label, single-arm cohorts.

Part I Cohort D and Part II Cohort E are open-label, randomized cohorts. Randomization will be performed by an IRT system, and participants will not be re-randomized.

Part III Cohorts G, H, I, J, K, L, M, and N are open-label, single-arm cohorts.

Study treatment will be dispensed at the study visits. Returned study treatment should not be re-dispensed to the participants.

In Part I, Cohort D, the randomization will be stratified by the following factor: Prior platinum + gemcitabine therapy (yes/no). Participants with prior gemcitabine will receive vinorelbine as control treatment if assigned to the control arm. Subjects with no prior gemcitabine will receive gemcitabine as control treatment if assigned to the control arm. Randomization to one of the two treatments will be at a 2:2:1 (the control being the smaller arm). Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Participants should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur within 3 days after randomization.

For Part II, Cohort E, the study site will be provided with the treatment arm to which the participant is assigned to from the IRT. Randomization to one of the two treatments will be at a 1:1 ratio. Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Participants should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 3 days after randomization.

6.3.2 Blinding

This is an open-label study, blinding procedures are not applicable.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose. This individual will write the date dispensed and participant number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

6.5 CONCOMITANT THERAPY

6.5.1 Permitted Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 30 days before screening until the *last* follow-up visit *(Table 2, Table 5, and Table 7)*

must be recorded along with reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency).

The Medical Monitor should be contacted if there are any questions regarding concomitant or previous therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

- All therapy and/or medication administered to manage AEs should be recorded on the Adverse Event eCRF.
- If any treatment is given within 30 days before screening, this should be recorded in the eCRF.
- Participants who experience infusion-associated symptoms may be treated symptomatically Section 8.3.8.
- Systemic corticosteroids and immune suppressants may attenuate potential beneficial immunologic effects of treatment with atezolizumab and *simlukafusp alfa* but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered.
- Megestrol administered as an appetite stimulant is acceptable while the participant is enrolled in the study.
- Use of limited field palliative radiotherapy is allowed at any time during the study. No delay of study treatment administration is foreseen although participants should not receive study treatment during radiation.

6.5.2 Prohibited Therapy

All medications (prescription and over-the-counter) taken within 30 days of study screening will be recorded appropriately in the eCRF. As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Administration of a live, attenuated vaccine during the study and 5 months after the last dose of atezolizumab is prohibited.

Use of the following therapies is prohibited during the study and for at least 21 days after the last dose of *simlukafusp alfa*:

- Investigational or unlicensed/unapproved agents
- Immunotherapy/radio-immunotherapy
- Chemotherapy

- Immunostimulatory agents (all participants, including those who discontinue the study early, should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab)
- Biologic agents (e.g., erlotinib)
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids, TNF-α inhibitors, mycophenolate, and other immune suppressants may be administered for the treatment of immune-related toxicities at the discretion of the treating physician after consultation with the Medical Monitor.

If any anti-neoplastic or investigational therapies listed above are needed, the participant will be considered to have evidence of progressive neoplastic disease and have experienced treatment failure with study treatment and should be withdrawn from study treatment.

Participants who experience a mixed response that requires local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, and/or radiofrequency ablation) for control of 3 or fewer lesions may still be eligible to continue study treatment. Participants who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor (see Section 7.1.1).

6.5.3 Chemotherapy Concomitant Therapy

Interactions common to all cytotoxic agents: Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR monitoring if it is decided to treat the participant with oral anticoagulants.

Please refer to the local SmPC for gemcitabine and vinorelbine for concomitant medication information associated with these treatments.

6.6 DOSAGE MODIFICATION

If, in the opinion of the Investigator, a toxicity is considered to be due solely to one of the study treatments, the dose of the other study treatments does not require modification. However, in cases potentially related to both drugs, treatment with both *simlukafusp alfa* and atezolizumab should be modified or permanently discontinued as appropriate based on the grade of toxicity. Examples of potentially overlapping toxicities that could be related to both drugs include immune-mediated toxicities; pulmonary toxicity, thrombocytopenia, and hepatic toxicity.

6.6.1 Dose Modification for *Simlukafusp Alfa*

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the participant's chart and recorded in the eCRF. The severity of AEs will be graded according to the NCI CTCAE v4.03 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to type of toxicity and the corresponding shift in toxicity grade, if the Investigator feels it is appropriate. For example, if a participant has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the Investigator to be unlikely to develop into serious or life-threatening events, treatment may be continued at the same dosage without reduction or interruption.

Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the clinically most relevant toxicity observed.

Dosage decrease of *simlukafusp alfa* will occur if participants experience the following:

- Hematological toxicities defined as:
  - Grade $\geq$ 4 neutropenia lasting longer than 48 hours
  - Grade $\geq$ 3 febrile neutropenia
  - Grade $\geq$ 4 thrombocytopenia lasting longer than 48 hours
  - Grade $\geq$ 3 thrombocytopenia associated with bleeding episodes.
- Any non-hematological toxicity Grade $\geq$ 3 including:
  - IRR, fever, or fatigue occurring systematically after each infusion compromising participant's quality of life.
  - Re-occurrence of liver test abnormalities (ALT and/or AST in combination with bilirubin 2 $\times$ ULN or 2 $\times$ baseline level).
  - CLS or signs and symptoms suggestive of CLS (e.g., edema, weight increase, hypoalbuminemia accompanied with protein in urine).

If a participant experiences toxicity as above, *simlukafusp alfa* will be held until the toxicities resolve.

Simlukafusp alfa administration will be held until resolution of toxicity NCI CTCAE Grade $\leq$ 2 hematological toxicities or Grade $\leq$ 1 non-hematological (in case of LFTs a resolution in participants with liver metastases to severity grade presented at baseline), toxicities (with the exception of toxicities considered as non-*simlukafusp alfa* related). If delay is due to immune-related AE, *simlukafusp alfa* can be resumed after resolution of immune-related AEs, if the Investigator and Medical Monitor agree on the participant's likely clinical benefit. If the treatment is interrupted due to atezolizumab-related event or other event (e.g., pharmacy error, participant unable to visit clinic due to non-medical

obstacle), *simlukafusp alfa* administration is to be given within 7 days from the planned dosing.

During the induction treatment phase in the QW/Q2W schedule, *simlukafusp alfa* is administered QW on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 2 Day 8. If toxicity from Cycle 1 Day 1 has not resolved until Cycle 1 Day 8 administration, the dosing on C1 Day 8 should be omitted, the participant followed as medically indicated and treatment resumed on Cycle 2 Day 1. The same omission rule applies to Cycle 2. If toxicity from the previous administration has not resolved during the maintenance phase, the treatment will be delayed until toxicity has resolved (as described in the paragraph above).

The selected dosing scheme (i.e., 10 mg) may be modified according to the tolerability requirements. Based on the observed toxicity profile in a cohort over time, other doses may be explored based on emerging data.

In the course of the treatment (during induction phase and/or maintenance phase), the dosage may be modified for an individual participant at any time to improve tolerability by reduction of *simlukafusp alfa* dose in 5 mg decrements down to the dose level of 5 mg. This will be done on the proposal of the Investigator after discussion with the Medical Monitor.

Further, a dosing scheme utilizing different doses and a different schedule of *simlukafusp alfa* (induction and/or maintenance phase) may be introduced at any time during the course of the study, on the basis of emerging data from this study and other studies, which investigate *simlukafusp alfa*. Depending on differences observed in previous studies (e.g., safety profile, PK differences, including drug-drug interactions), doses may be altered, but not to exceed 20 mg *simlukafusp alfa*.

6.6.2 Dose Modification for Administration of Atezolizumab

No dose reductions of atezolizumab are recommended.

Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks and adverse event management guidelines for atezolizumab.

6.6.3 Dose Modification for Administration of Gemcitabine and Vinorelbine

Myelosuppression is the principal DLT with gemcitabine. For further details regarding risks and adverse reactions following gemcitabine administration, see the local prescribing information for gemcitabine.

All participants receiving vinorelbine should be monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting, with granulocyte nadirs occurring between 7 and 10 days after dosing and granulocyte count recovery usually

within the following 7 to 14 days. Vinorelbine should not be administered to participants with granulocyte counts $<$1,000 cells/mm^3. For further details, see the local prescribing information for vinorelbine.

6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide *simlukafusp alfa* or any other study treatments or interventions to the participants after the end of the study or when participants discontinue or have been withdrawn from the study. The Sponsor will evaluate whether to continue providing study treatment to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1 Regulatory, Ethical, and Study Oversight Considerations.

7.1 DISCONTINUATION OF STUDY TREATMENT

See the SoAs (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Participants must discontinue study treatment if they experience any of the following:

- Pregnancy
- Grade 4 IRR for *simlukafusp alfa* and atezolizumab
- Grade 3 IRR for atezolizumab
- IgE-mediated hypersensitivity reactions, including anaphylaxis
- Dose reduction and delays for gemcitabine and vinorelbine as per the local SmPC
- Any toxicity which is not manageable with dose delays (as allowed per protocol), dose decrease and appropriate treatment (see Appendix 9)
- Disease progression when there is a consensus that the participant will not benefit from study treatment

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/discontinuation visit (see Section 8.10.3) and may undergo

follow-up assessments (see Section 8.10.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

7.1.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator or Sponsor), a temporary treatment interruption should be considered. Participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified in the opinion of the Investigator.

Further, if a participant has achieved clinical benefit (i.e., durable disease control with SD, PR, or complete response [CR]), as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy result (if available), and clinical status and if the participant is on treatment beyond the 1.5-fold duration of the expected median PFS for the respective cohort and clinical setting, the study treatment may be paused at the discretion of the Investigator after consultation with the Medical Monitor. While the treatment is paused, assessments per SoA will be suspended, except for tumor assessments. Restarting the study treatment should be considered as soon as medically justified in the opinion of the Investigator. During treatment pause, the participant remains on study and is followed according to the respective SoA table for up to 2 years or until the study closes.

If during the treatment pause, the participant's disease becomes uncontrolled and/or progresses, the study treatment may be reintroduced after consultation with the Medical Monitor if the study is still open. PK and ADA samples should be collected predose and at the end of the infusion (PK only) on the day that the treatment is reintroduced. For the remaining samples, the SoA shall be followed according to the "Subsequent cycles" category. PD samples should be collected according to the guidance for an unscheduled visit.

If the participant's disease becomes uncontrolled and progresses during the treatment pause and the participant does not wish to resume study treatment, a biopsy may still be taken if the participant consents.

Participants who experience a mixed response that requires local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, and/or radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. For such cases, a longer drug interruption period is allowed.

See Section 6.6.1 for dose modification information.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants will be treated with *simlukafusp alfa* in combination with atezolizumab or with gemcitabine or vinorelbine monotherapy until disease progression, unacceptable

toxicity, or withdrawal of consent*, or for a maximum of 24 months. In case the participant has reached the defined duration and continues to derive benefit, a longer treatment duration might be granted by the Sponsor.* If *simlukafusp alfa* treatment is discontinued, treatment with atezolizumab can be continued, or vice versa, under the following conditions:

- If, and as long as, the participant experiences benefit in the opinion of the Investigator
  - OR
- Until unacceptable toxicity or symptomatic deterioration develops, which is attributed to disease progression as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status
  - OR
- Withdrawal of consent.

If a participant experiences CR, as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, the study treatment may be discontinued at the discretion of the treating physician after consultation with the Medical Monitor. The participant may remain on study and be followed according to the SoA (Section 1.3). If the disease reappears after CR, the study treatment may be reintroduced after consultation with the Medical Monitor. As with other immunotherapies, treatment beyond RECIST v1.1 progression could be considered after approval of the Sponsor.

The criteria below are needed for continuing treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation):

- Absence of clinical deterioration and Investigator-assessed potential clinical benefit for the participant.
- The participant is tolerating study treatments.
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

Participants 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 participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed-up for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested before withdrawal, results from those tests will remain as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study who are not evaluable for response will be replaced.

See the SoAs (Section 1.3) for data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoAs (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time-frame defined in the SoA.

Samples for laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

On the basis of continuous analysis of the data in this study, and that of Studies BP29842 and BP39365 and others, any sample type or biomarker evaluation not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

8.1 ACTIVITY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Tumor response will be evaluated according to both RECIST v1.1 (see Appendix 7). Response will be assessed by the Investigator on the basis of physical examinations and CT scans (or magnetic resonance imaging [MRI]) of chest, abdomen, and pelvis as defined in the SoA (Section 1.3). CT scans of the neck should be included, if clinically indicated. Ultrasound and x-rays are not acceptable for monitoring target lesions. All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Consistency of consecutive CT scans (or MRIs) should be ensured during all assessments for each participant; the same method of assessment (preferable also by same evaluator) and the same technique must be used to evaluate lesions throughout the entire study. Use of CT (or MRI) is required for baseline lesions $<$20 mm and must be documented in medical records and used consistently throughout the study. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans). Tumor measurements should be made by the same Investigator/Radiologist for each participant during the study to the extent that this is feasible. At the Investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photos must include a ruler for documentation purposes.

The data collected for RECIST v1.1 will be used by the Sponsor to calculate programmatically timepoint responses for modified RECIST for immune-based therapies (iRECIST; Appendix 8), a recently published set of guidelines developed by the RECIST

working group in an effort to harmonize immune-based response criteria across the academic and industrial cancer immunotherapy field (Seymour et al 2017).

Because of possible delayed onset of tumor response associated with immunotherapy treatment, as well as borderline progression, apparent radiologic progression with improving clinical status or mixed responses, in the absence of clinical deterioration, any initial assessment of radiological progressive disease should be confirmed by a repeat evaluation at the next timepoint for tumor assessment. As with other immunotherapies, treatment beyond RECIST progression could be considered after approval of the Sponsor. The criteria needed for continuing treatment beyond initial apparent progressive disease (e.g., radiological progression secondary to tumor inflammation) are described in Section 7.2.

In addition to investigator site assessment, tumor assessment may also be performed centrally by an independent reviewer for prospective and retrospective analysis.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoAs (Section 1.3).

The safety plan for patients in this study is based on clinical experience with simlukafusp alfa and atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 8.3.8 and Section 8.3.9).

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 simlukafusp alfa and atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Section 6.6, Section 7.1, and Appendix 9. Refer to Section 8.3, Appendix 2, Appendix 3, and Appendix 5 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 COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history,

appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgement. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

8.2.1 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History eCRF. A physical examination will include careful attention to areas of known and possible malignancy. The physical examination includes weight. For the study, the same calibrated balance should be used at site. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

8.2.2 ECOG Performance Status/Karnofsky Performance Score

Performance Status will be measured by using the ECOG or KPS. Performance Status will be assessed with each physical examination, before each study treatment administration, and at the safety follow-up visits. It is recommended, where possible, that a participant's Performance Status will be assessed by the same person throughout the study.

8.2.3 Chest X-Ray

Chest x-ray will be performed at Screening/Baseline, and as clinically indicated to establish the baseline level for any potential future sign of pulmonary toxicity, in particular pulmonary edema.

8.2.4 Medical History and Demographic Data

Medical History includes clinically significant diseases, surgeries, cancer history (including previous cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days before the screening visit. PD-L1 status information, as available in the participant's record, should also be reported.

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

8.2.5 Vital Signs

Routine vital signs including seated or supine diastolic and systolic blood pressure, pulse rate, pulse oximetry, respiratory rate, and body temperature will be assessed as specified in the SoAs (Section 1.3). These should be measured after at least 5 minutes of sitting or lying supine (consistency should be maintained for an individual participant).

Spirometry (FEV and FVC) (global initiative for obstructive lung disease level classification) will be performed at screening and as clinically indicated. Unscheduled assessments should be recorded as appropriate in the eCRF.

Participants experiencing Grade ≥3 vital signs abnormalities at a previous cycle should stay at site at the next study treatment administration for at least 24 hours post-infusions. In case of drop in blood pressure associated with hemodynamic instability and/or abnormal heart rate, particularly arrhythmia, *simlukafusp alfa* or atezolizumab administration should be interrupted and the participant should be fully monitored until normal cardiac function is regained.

8.2.6 Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures the PR interval, QRS, QT, and QTc intervals.

To minimize variability, it is important that participants be in a resting position for ≥10 minutes before each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed before any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction), QTcF (Fridericia's correction), and RR will be recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in 2 categories: absent/normal or abnormal.

8.2.7 Transthoracic Echocardiogram or Multiple-Gated Acquisition Scans

TTE or MUGA scans will be performed according to the timepoints specified in the SoA (see Section 1.3). This may be further repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. The TTE or MUGA should be performed at the 28 day follow-up visit if clinically indicated based on the results from the discontinuation

visit. TTE or MUGA scans will be used to monitor the cardiac parameters of function (i.e., left ventricular ejection fraction).

8.2.8 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual, site's local laboratory requirements (where applicable), and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the cause should be identified and the Sponsor notified.
- If laboratory values from non–protocol-specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Additional samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety. Any remaining samples from these collections may also be used for additional exploratory research.

Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious AESIs and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity, and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, 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 as follows:

After informed consent has been obtained, but before initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until 3 months after the last dose of study treatment or until the initiation of a post-study anti-cancer treatment, whichever occurs first.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (defined as 3 months after the last dose of study treatment).

However, if the Investigator learns of any SAE (including an AE leading to death) or other AEs of concern that are believed to be related to previous treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, non-serious AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, EC/IRB, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the EC/IRB, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, and EC/IRB, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Medical Monitor's contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 4 months after the last dose of *simlukafusp alfa*, or for 5 months after last dose of atezolizumab (whichever is longer).

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 2 months after the last dose of *simlukafusp alfa*.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious AESIs 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 Appendix 2 for reporting instructions).

Non-serious AESIs for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

Non-serious AESIs specifically related to atezolizumab:

- Conditions that may be suggestive of an autoimmune disorder, including the following:

– Pneumonitis
– Colitis
– Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, *hypothyroidism/*hyperthyroidism, or hypophysitis
– Hepatitis, including AST or ALT $>10\times$ULN
– Systemic lupus erythematosus
– Neurologic: Guillain-Barré syndrome, myasthenia gravis/myasthenic syndrome, meningoencephalitis
– Nephritis
– Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome (SIRS), *hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)*
– Ocular toxicities (e.g., uveitis, retinitis*, optic neuritis*)
– Myositis
– Myopathies, including rhabdomyolysis
– Grade $\geq$2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
– Vasculitis
– Autoimmune hemolytic anemia
– Severe cutaneous adverse reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

No disease-related events are expected for this study.

8.3.8 Management of Specific Adverse Events

8.3.8.1 Management of Specific Adverse Events Related to *Simlukafusp Alfa*

Always refer to the latest *Simlukafusp alfa* Investigator's Brochure for the complete information. The current *simlukafusp alfa* Investigator's Brochure provides the full and most up-to-date information about all risks and risk mitigation measures related to *simlukafusp alfa*.

Management of specific AEs for *simlukafusp alfa* is provided below. The safety management guidelines for atezolizumab are provided in Appendix 9. The suspected causality of the event in question should inform which guidance is to be followed. If it is unclear which treatment the event should be attributed to, the most conservative approach should be used. When in doubt, contact Medical Monitor.

Infusion-Related Reactions

Administration of therapeutic antibodies may cause IRRs characterized by symptoms such as fever, chills, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnea, headache, tumor pain, nausea, and/or vomiting. Respiratory and cardiac symptoms, such as bronchospasm, larynx, and throat irritation, wheezing, laryngeal edema and atrial fibrillation, may also occur. Such reactions typically occur during or shortly after an infusion or within 24 hours after study treatment infusion, predominantly at the first infusion. The incidence and severity typically decrease with subsequent infusions.

Participants may also develop immunoglobulin E (IgE)-mediated hypersensitivity reactions to atezolizumab, or *simlukafusp alfa*. IRRs may be indistinguishable from an anaphylactic reaction; however, in case of IgE-mediated hypersensitivity, symptoms typically occur after previous exposure and very rarely with the first infusion. In case of confirmed IgE-mediated hypersensitivity reaction, treatment should be permanently discontinued.

In case of Grade 4 IRR related to atezolizumab, or *simlukafusp alfa*, the participant should be withdrawn from the study treatment.

It is mandatory to follow all instructions with regard to premedication, dosage rate, and discontinuation rules described in the Section 6.1. Infusion-related reactions are also described as an AESI for atezolizumab in Section 8.3.6.

Management of Infusion-Related Reactions

Participants who experience an IRR with Cycle 1 of *simlukafusp alfa* may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 13. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 13 Management Guidelines for Infusion-Related Reactions

Event	Action to Be Taken
Grade 1 IRR	• Reduce infusion rate to half the rate being given at the time of event onset. • Monitor participant until symptoms resolve completely. • After the event has resolved, the Investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
Grade 2 IRR	• Interrupt infusion. • Administer symptomatic treatment as needed. • Monitor participant until symptoms resolve completely. • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For the subsequent infusion, administer pre-medication as per the guidelines in the Premedication Section (Section 6.1.5.1).
Grade 3 IRR	• Interrupt infusion. • Administer symptomatic treatment, as needed, including corticosteroids. • Monitor participant until symptoms resolve completely. • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For the subsequent infusion administer premedication as per the guidelines in the Premedication Section (Section 6.1.5.1).
Grade 4 IRR OR Anaphylaxis to *simlukafusp alfa*, Grade 3 or 4	• Stop infusion. • Administer symptomatic treatment as needed, including corticosteroids • Monitor participant until symptoms resolve completely. • Permanently discontinue *simlukafusp alfa* and contact Medical Monitor.

IRR = infusion-related reaction.

Capillary Leak Syndrome

CLS can be a severe and potentially fatal event. One Grade 4 case of CLS has been reported in a participant with NSCLC treated with cergutuzumab amunaleukin (carcinoembryonic antigen-targeted IL-2v) in combination with atezolizumab (Cergutuzumab Amunaleukin Investigator's Brochure).

The toxicities of IL-2 therapy (e.g., aldesleukin) are thought to result primarily from CLS. The most frequent and earliest clinical manifestations include edema, weight gain, hypoalbuminemia, oliguria, hypotension, tachycardia, and/or dyspnea, ultimately leading to organ failures. The organs that are particularly affected are the heart, lungs, kidneys, and CNS. Complications, such as pulmonary congestion/edema, pleural effusion, ascites, cardiovascular manifestation, and early signs of renal failure, have been

reported. Participants may also experience chills, fever, malaise, and pain in the extremity (due to edema).

For further details on IL-2-mediated CLS, see Schwartzentruber 2001, Schwartz et al. 2002, Proleukin® U.S. Package Insert, and Proleukin® EU Summary of Product Characteristics. Table 14 provides guidelines for management of CLS.

Table 14 Guidelines for Managing Capillary Leak Syndrome and Associated Signs and Symptoms

Event	Action Recommended for the Management of Symptoms
General recommendations	Delay *simlukafusp alfa* administration. Consider admission to an intensive care unit depending on severity of symptoms. Medical management of CLS involves careful monitoring of the patient's fluid and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ function, which includes assessment of mental status and urine output. Hypovolemia is assessed by catheterization and central pressure monitoring (Proleukin USPI).
Severe capillary leak	In cases of severe capillary leak, there is marked disruption of endothelial cell-to-cell binding resulting in massive losses of protein-rich fluid into the interstitial space. Hypotension, shock, and AKI often dominate the initial clinical picture. In these patients, the priority is to increase the blood pressure in order to maintain sufficient organ perfusion. • The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that stabilizes blood pressure. • A fluid-restrictive strategy is advocated to limit interstitial fluid volume overload. • The next step in the management of persistent hypotension is the administration of vasopressors. • A trial of 25% albumin IV is an additional option, although its efficacy is limited in those with a severe capillary leak. • In addition to fluid therapy, steroid therapy has demonstrated efficacy in CLS (Siddall et al 2017); the use of steroids can be considered at the investigators' discretion. Use of oral prednisolone 1 mg/kg has been reported (Stirling 1998). • Supportive care with invasive and non-invasive ventilation as well as renal replacement may be necessary in severe cases (Siddall et al 2017). • In case of progressive shortness of breath, endotracheal intubation or drainage of pleural effusion may be required.

Table 14 Guidelines for Managing Capillary Leak Syndrome and Associated Signs and Symptoms (cont.)

Event	Action Recommended for the Management of Symptoms
Recovery phase or mild capillary leak	In cases of mild capillary leak or during the recovery phase from severe capillary leak, the endothelial injury is less severe, resulting in stable blood pressure. In this setting, fluid overload symptoms are predominant (e.g., pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). • Volume removal with loop diuretics is the primary therapy in these patients. • In patients with low blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. • Patients with AKI refractory to diuretics will require renal replacement. (Siddall et al 2017).
Additional recommendations	
Oliguria management	• Delay *simlukafusp alfa* administration in case of Grade 3 urine output decrease (<80 mL in 8 hours) • Use fluids judiciously if increase in urine output is required • Consider use of catecholamines/alpha-adrenergic vasopressors according to institutional recommendations
Gastrointestinal toxicity	• Plan premedication with dopamine antagonist if moderate to severe nausea and/or vomiting occurs; provide alternative antiemetic for breakthrough nausea and/or vomiting. Do not use corticosteroids as anti-emetics • Use H2-receptor antagonist prophylactically to minimize epigastric pain • Treat diarrhea with anti-motility agents (e.g., loperamide) • Encourage patient to eat small, frequent meals
Neurotoxicity	• Delay treatment if persistent confusion, disorientation, hallucinations, progressive agitation, or somnolence unrelated to concomitant medication occurs. • If symptoms reoccur, permanently discontinue therapy. • Therapy may be resumed after symptoms resolve, and only if no Grade 4 toxicity has occurred.
Laboratory abnormalities	• Electrolytes and minerals: frequently require correction • Anemia and thrombocytopenia: may require transfusion • Transient cholestasis should be monitored until resolution. • Asymptomatic elevations in cardiac isoenzymes may represent risk for myocarditis and should be further monitored before next administration of *simlukafusp alfa*. • Hypothyroidism: may require hormone replacement.

AKI = acute kidney injury; CLS = capillary leak syndrome; IV intravenously.

Siddall E, Khatri M, and Radhakrishnan J. Capillary leak syndrome:ertiologies, pathophysiology, and management. Kidney Int. 2017;92(1):37-46.

Hematological Toxicities

Guidance for the management of hematologic toxicities is provided in Table 15.

Table 15 Guidelines for Managing Hematological Toxicities

Event	Action to Be Taken
Grade 1 or 2, or a medically meaningful decrease from baseline	• *Simlukafusp alfa* may be continued at the investigator's discretion. • If *simlukafusp alfa* is withheld: If the event resolves and the Medical Monitor agrees that *simlukafusp alfa* should be continued, resume *simlukafusp alfa*. If not, consider if permanent discontinuation of *simlukafusp alfa* is necessary.
Grade 3 event other than thrombocytopenia associated with bleeding or febrile neutropenia	• *Simlukafusp alfa* may be continued at the investigator's discretion. • If *simlukafusp alfa* is withheld: If event resolves and Medical Monitor agrees that *simlukafusp alfa* should be continued, resume *simlukafusp alfa*. If not, permanently discontinue *simlukafusp alfa*.
Grade 3 thrombocytopenia associated with bleeding or Grade 3 febrile neutropenia	• *Simlukafusp alfa* may be continued at the investigator's discretion; if continued, the dose should be reduced. [a,b] • If *simlukafusp alfa* is withheld: If event resolves and Medical Monitor agrees that *simlukafusp alfa* should be continued, resume *simlukafusp alfa* and consider reducing the dose. [a,b] If not, permanently discontinue *simlukafusp alfa*.
Grade 4	• *Simlukafusp alfa* may be continued at the investigator's discretion; if continued, the dose should be reduced. [b,c] • If *simlukafusp alfa* is withheld: If event resolves and Medical Monitor agrees that *simlukafusp alfa* should be continued, resume *simlukafusp alfa* and consider reducing the dose. [a,b] If not, permanently discontinue *simlukafusp alfa*.

IRR = infusion-related reaction; NSAID = non-steroidal anti-inflammatory drug.

[a] The dose of *simlukafusp alfa* can be reduced to 5 mg for the management of drug-related toxicities and must be discontinued thereafter if further dose reduction is necessary.

[b] After dose reduction, the dose of *simlukafusp alfa* may be adjusted back to the previous of 10 mg dose with Medical Monitor approval.

[c] Resumption or reduction in the dose of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement.

Liver Enzyme Elevation

ALT and/or AST are the most sensitive markers for hepatocyte stress. Most patients will likely experience liver enzyme elevation with an initial rise in ALT/AST, which may be followed by a transient increase in bilirubin. The transaminitis should start decreasing 7 days after administration and total bilirubin should decrease with a few days' delay. Table 16 provided guidelines for the management for liver enzyme elevation.

Table 16 Guidelines for Managing Liver Enzyme Elevation

Event	Action to Be Taken	Workups
Grade 1 ALT and/or AST (>ULN - 3.0 x ULN if baseline normal; 1.5 - 3.0 x baseline if baseline abnormal) OR **Grade 1 BILI** (>ULN - 1.5 x ULN if baseline normal; > 1.0 - 1.5 x baseline if baseline abnormal)	• Continue *simlukafusp alfa* treatment, monitor closely until resolution to baseline or Grade <1	• Monitor LFTs as needed. Consider repeat LFTs testing within 48-72 hours after detection of LFT elevation
Grade 2 ALT and/or AST (>3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline if baseline abnormal) **Grade 1 BILI** (>ULN - 1.5 x ULN if baseline normal; > 1.0 - 1.5 x baseline if baseline abnormal)	• Hold *simlukafusp alfa* treatment until resolution to baseline or Grade 1 • If concomitant with Grade 1 bilirubin elevation, review other possible contributing factors: medications (statins, antibiotics, EtOH)	• Monitor LFTs, INR, albumin every 2 days • If persistent for >48 hours – Rule out infection (e.g., perform Hep A, B, C, D, or E serology/PCR) – Monitor auto-antibodies (e.g., anti-ANA, SMA, SLA/LP, LKM-1, LCI) – Consider imaging – Consider referral to hepatologist – Consider differential diagnosis with autoimmune hepatitis, new hepatic metastases, hepatic vein thrombosis hepatic toxicity due to other drugs or substances. alcoholic liver disease; systemic infection or sepsis; Wilson's disease, heritable liver diseases including cystic fibrosis; muscle injury (rhabdomyolysis); ischemic hepatopathy; biliary tract

Event	Action to Be Taken	Workups
		disease. – If a subject has Grade 2 or greater liver function test abnormalities, then evaluate for the following to exclude other causes of acute or chronic liver disease based: Serologies for hepatitis A, B, C, D, and E (acute or chronic); Autoimmune hepatitis; Doppler ultrasound to rule out biliary obstruction, new hepatic metastases, and hepatic vein thrombosis; Hepatic toxicity due to other drugs or substances such as acetaminophen, substance abuse (cocaine, opiates, herbal drugs); Alcoholic liver disease; Systemic infection or sepsis; Wilson's disease, heritable liver diseases including cystic fibrosis; Muscle injury (rhabdomyolysis); Ischemic hepatopathy; Biliary tract disease.
Grade 2 ALT and/or AST (>3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline if baseline abnormal) **Grade 2 BILI** (>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal)	• Hold *simlukafusp alfa* treatment until resolution to baseline or Grade 1 • If persistent with concomitant Grade 2 bilirubin elevation which does not resolve within 5 days, start equivalent of methylprednisolone PO 0.5–2 mg/kg/day until resolution commences • If steroids are needed for more than 72 hours, taper should occur over 4 weeks. After a short course of steroids (e.g., ≤72 hours), the taper period may be shortened • If the event does not resolve to baseline or Grade 1, permanently discontinue *simlukafusp alfa* • If Hy's law criteria are met (ALT or AST >3 × ULN and total bilirubin (TBL) >2 × ULN or INR >1.5 in absence of cholestasis and other reasons for LFTs	• Workup as above

Event	Action to Be Taken	Workups
	elevations are excluded), at the first occurrence of the event and provided that LFT abnormalities resolve spontaneously within one week and no treatment is required, treatment continuation with *simlukafusp alfa* is allowed; dose reduction to 5 mg is recommended. Treatment continuation should only be attempted on an individual participant basis, following approval from Medical Monitor, if the investigator believes that the potential benefits for the participant outweigh the potential risks. • If Hy's law criteria are met (ALT or AST >3 × ULN and TBL >2 × ULN or INR >1.5 in absence of cholestasis and other reasons for LFTs elevations are excluded) and the participant has protracted clinical course (i.e., >1 week) or requires for treatment with corticosteroids and/or mycophenolate mofetil, it is recommended to permanently discontinue treatment. • At the second occurrence of LFTs elevation meeting Hy's law criteria, it is recommended to permanently discontinue treatment. • Contact the Medical Monitor	

Event	Action to Be Taken	Workups
Grade 3 ALT and/or AST (>5.0 - 20.0 x ULN if baseline normal; >5.0 - 20.0 x baseline if baseline abnormal) **Grade 2 BILI** (>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal) OR **Grade 3 BILI** (>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal)	• Hold treatment until resolution to baseline or Grade 1 • If no improvement after 24 hours, administer methylprednisolone IV (0.5-2 mg/kg/day) until Grade 2, then taper over 4 weeks. After a short course of steroids (e.g., ≤72 hours), the taper period may be shortened • In case of isolated ALT/AST elevation, consider not initiating steroids treatment for 48 hours • If the event does not improve within 72 hours after initiation of corticosteroids, consider addition of an alternative immunosuppressive agent (e.g., mycophenolate mofetil [500–1,000 *mg* BID] to the regimen) • Contact Medical Monitor • Consider dose reduction or discontinuation of *simlukafusp alfa* • If the event does not resolve to baseline or Grade 1, permanently discontinue *simlukafusp alfa*. • If Hy's law criteria are met (ALT or AST >3xULN and TBL >2xULN or INR >1.5 in absence of cholestasis and other reasons for LFTs elevations are excluded), at the first occurrence of the event and provided that LFT abnormalities resolve spontaneously within one week and no treatment is required, treatment continuation with *simlukafusp alfa* is allowed; dose reduction to 5 mg is recommended. Treatment continuation should be attempted only on an individual participant basis, following approval from Medical Monitor, if the investigator believes that the potential benefits for the participant outweigh the potential risks. • If Hy's law criteria are met (ALT or AST >3xULN and TBL >2xULN or INR >1.5 in absence of cholestasis	• Workup as above • Track Ferritin and CRP • Measure sCD25

Event	Action to Be Taken	Workups
	and other reasons for LFTs elevations are excluded) and the participant has protracted clinical course (i.e., >1 week) or requires for treatment with corticosteroids and/or mycophenolate mofetil, it is recommended to permanently discontinue treatment • At the second occurrence of LFTs elevation meeting Hy's law criteria, it is recommended to permanently discontinue treatment. • In case of ALT or AST >8xULN at any point or ALT or AST >5xULN for more than 2 weeks (regardless of bilirubin values), it is recommended to permanently discontinue treatment.	
Grade 4 ALT and/or AST (>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal) **Grade 4 BILI** (>10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal)	• Administer Methylprednisolone IV (0.5-2 mg/kg/day) until Grade 2, then taper steroids over 4 weeks. After a short course of steroids (e.g., ≤72 hours), the taper period may be shortened • If no improvement after 48 hours, consider treatment with mycophenolate (500–1,000 mg BID) • It is recommended to permanently discontinue treatment. • Contact Medical Monitor	• Consider a liver biopsy • Consult a hepatologist to establish etiology of hepatic injury.

AE = adverse event; ANA = antinuclear antibodies; ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = bis in die (twice daily); BILI = bilirubin, CRP = C reactive protein; EtOH = ethyl alcohol; Hep = hepatitis; LCI = LFT = liver function test, LKM-1 = INR = international normalized ratio, ULN = upper limit of normal; sCD25 = soluble CD25; SLA/LP = anti-soluble liver antigen/liver-pancreas; SMA = smooth muscle antibodies; TBL = total bilirubin.

Pyrexia

Participants may experience isolated fever (i.e., pyrexia) accompanied by symptoms, such as chills, within 24 hours after *simlukafusp alfa* infusion as a single-agent or in combination and not be accompanied by other IRR-like symptoms as described above. In that case, the AEs should be reported individually and not as an IRR.

Premedication with antipyretics is *recommended*, including before the first infusion, according to standard practice or at the discretion of the investigator. In addition, pyrexia can be treated efficiently with paracetamol in the majority of cases.

Consequently, Investigators should provide guidance to participants for the management of isolated episode of fever (no other signs and symptoms); in particular, participants should regularly check their body temperature during the days after each administration of *simlukafusp alfa* and take early intervention with standard anti-pyrexia treatments (e.g., paracetamol and non-steroidal anti-inflammatory drugs), as current practice.

8.3.8.2 Management of Specific Adverse Events Related to Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, myositis*, and severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome*, which are considered to be potential risks for atezolizumab*. For a detailed description of anticipated safety risks for atezolizumab, refer to Appendix 9 and the atezolizumab IB (Section 6). Guidelines for managing participants who experience anticipated AEs, including criteria for treatment interruption or discontinuation, are provided in Appendix 9.

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 cause.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit-risk balance a given participant may be experiencing before further administration of atezolizumab. In participants who have met the criteria for permanent discontinuation, resumption of atezolizumab may be

considered if the participant is deriving benefit and has fully recovered from the immune-related event. Participants can be re-challenged with atezolizumab only after approval has been documented by the Investigator (or an appropriate delegate) and the Medical Monitor.

8.3.8.3 Gemcitabine and Vinorelbine Dose Modification and Management of Specific Adverse Events

Please refer to the SmPC for the most up-to date information regarding AEs and AE management.

8.3.9 Overlapping Toxicities

The following toxicities are considered potentially overlapping in this trial:

- Infusion-related reactions: all study treatments may potentially provoke IRRs and/ or immediate hypersensitivity reactions.
- Immune-mediated toxicities: the influence of *simlukafusp alfa* on atezolizumab-related immunotoxicity is unknown but, on the basis of the mechanism of action, the risk is expected to be low. Participants will be carefully monitored for signs and symptoms of immune-mediated reactions.
- Severe cutaneous toxicity: Stevens-Johnson syndrome (SJS) is a described risk for atezolizumab. An event of SJS occurred in a patient receiving *simlukafusp alfa* in combination with atezolizumab (see *Simlukafusp Alfa* Investigator's Brochure). For management guidelines for dermatologic events related to *simlukafusp alfa* and/or atezolizumab see Table 17.
- Hematological toxicities: thrombocytopenia has been reported with both study treatments. Participants will be carefully monitored for platelets and treated if necessary.
- Abnormal liver tests: abnormal LFTs are a known risk for IL-2 and liver toxicity has been reported with atezolizumab. There is an identified risk of overlapping toxicity between *simlukafusp alfa* and atezolizumab for liver effects, as described in the *Simlukafusp Alfa* Investigator's Brochure.

All recommendations regarding prophylaxis and management of these toxicities must be observed as described in the relevant paragraphs of this section.

Table 17 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue *simlukafusp alfa*/atezolizumab • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue *simlukafusp alfa*/atezolizumab. • Consider participant 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.
Dermatologic event, Grade 3	• Withhold *simlukafusp alfa*/atezolizumab for up to 12 weeks after event onset. [a] • Refer participant 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 *simlukafusp alfa*/atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding *simlukafusp alfa*/atezolizumab, permanently discontinue *simlukafusp alfa*/atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue *simlukafusp alfa*/atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	*Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:* • *Withhold simlukafusp alfa/atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens Johnson syndrome or toxic epidermal necrolysis, permanently discontinue simlukafusp alfa/atezolizumab.*

[a] *Simlukafusp alfa*/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 agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of *simlukafusp alfa*/atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. Participants can be re-challenged with *simlukafusp alfa*/atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dosage being studied. An overdose or incorrect administration of study

treatment is not an AE unless it results in untoward medical effects (see Appendix 2 for further details).

Decisions regarding dosage interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor on the basis of the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis as soon as possible.
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

8.5 PHARMACOKINETICS

All blood samples for PK assessment will be collected from an IV line from the arm opposite to that used for study treatment administration. The PK assessments will be performed as outlined in the Main SoAs and Detailed SoAs (see Section 1.3).

The date and time of each sample collection will be recorded in the eCRF. The procedures for the collection, handling, and shipping of PK samples can be found in the separate central laboratory manual. *Simlukafusp alfa* and atezolizumab levels will be analyzed by using validated assays.

During the course of the study, PK sampling timepoints may be modified on the basis of emerging data to ensure the PK of *simlukafusp alfa* and atezolizumab can be adequately characterized.

Additional PK samples will be taken at the time of treatment discontinuation, if the participant experiences an IRR, or if the participant experiences an AE leading to dose-reduction or -delay of *simlukafusp alfa* or atezolizumab administration (see Section 6.6).

Remaining PK sample volume may be used for additional ADA analysis, exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays after the mentioned intended uses.

The PK samples will be destroyed within 6 months after the date of bioanalytical report only after Sponsor approval.

8.5.1 Immunogenicity Assessments

Although *simlukafusp alfa* and atezolizumab are humanized antibodies, there is a risk that ADAs against *simlukafusp alfa* or atezolizumab could develop, potentially reducing their activity/efficacy, potentially resulting in symptomatic hypersensitivity reactions, in particular immune-complex reactions, or both.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against *simlukafusp alfa* and atezolizumab at multiple timepoints before, during, and after treatment.

Additional ADA samples will be drawn at the time of treatment discontinuation or at the safety follow-up visits and in participants who experience a Grade $\geq$2 IRR and in participants with clinical signs of hypersensitivity reaction, in particular immune-complex reactions.

In any case, for each collected ADA sample, a corresponding PK sample will be collected at the same timepoint for the determination of the *simlukafusp alfa* and/or atezolizumab concentrations.

Remaining ADA sample volume may be used for additional exploratory characterization, biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays (e.g., PK) after the mentioned intended uses.

The ADA samples will be destroyed within 6 months after the date of bioanalytical report only after Sponsor approval.

Details on sampling procedures, sample storage, and shipment are documented in the Sample Handling Manual.

8.6 PHARMACODYNAMICS

8.6.1 Blood Samples

The following samples will be collected as specified in the Main SoAs and Detailed SoAs (Section 1.3) for PD and exploratory biomarker assessments:

- Whole blood samples: Whole blood samples will be collected for flow cytometry (FACS Basic and FACS Advanced).
- Plasma samples: Blood for plasma isolation (blood for PD plasma) will be collected according to the SoAs, at the time of an IRR, and at unscheduled and the safety follow-up visits. Cytokines and inflammation markers may be measured in these samples. Cytokine measurements, except for sCD25, will only be conducted if safety and/or activity rationales develop. In addition, in case of IRR(s), an assessment of cytokines released during the reaction will be done on plasma samples from the time of the IRR. The plasma sample used for these PD analyses will be used for cytokine release at IRR and IgE and tryptase assessment.

- Additional plasma samples are collected to allow the assessment of tumor mutation burden in peripheral blood.
- Serum samples: Blood for serum isolation (blood for PD serum) will be collected according to the SoAs and at the 28-day Follow-Up Visit (see Section 1.3). Additional soluble markers, such as soluble FAP, will be measured in these samples if activity rationale develops.
- Part III only: An additional plasma and serum sample will be collected at Cycle 1 Day 1 for central testing of EBV and high-risk HPV status.

8.6.2 Tumor Tissue Samples

To mitigate the potential risk associated with tumor biopsies, all participants (where applicable) must have tumor lesions from which biopsies can be safely obtained, as per clinical judgment of the treating physician. Baseline and on-treatment biopsies should preferably be collected from the same lesion. Biopsies are scheduled such that both the extent and the duration of immune cell activation in the target tissue can be investigated in this study.

- Biomarkers related to the mode-of-action of *simlukafusp alfa* in combination with atezolizumab will be analyzed. Tumor tissue samples may also be used for research purposes to test hypotheses of response prediction or resistance markers. Two types of tumor tissue samples will be collected, fresh and archival, as described below:
- Archival Tumor Tissue Samples: Formalin-fixed, paraffin-embedded (FFPE) archival tumor tissue is to be obtained from all participants (within 2 months of enrollment)

  These samples should preferably come from the primary tumor (previous metastasis is acceptable) and should include the invasive margin, if possible. The archival specimen must contain adequate viable tumor tissue to establish PD-L1 expression status by a central laboratory.

  These samples will also be used to correlate FAP expression and lymphocyte infiltration in the primary tumor (or previous metastasis) and the current metastasis. Mismatch repair status may be also analyzed in these samples.

  Archival tumor blocks will be returned to the sites unless the site explicitly requests for Roche to not return the archival block. In the event the archival block is not returned to the site, blocks will be destroyed at Roche discretion or transferred to RBR if participant provided consent.

  For Part II Cohort E only, study enrollment will be based on confirmed PD-L1 status (TPS $\geq$ 50%) assessed locally (or centrally in case local testing is not possible) on mandatory archival tissue (or fresh biopsy if archival not available). Archival tumor tissue also should be shipped to a central laboratory for confirmational PD-L1 testing as instructed by the laboratory manual.

- Freshly Collected Tumor Biopsy Samples

In CPI-naïve NSCLC participants (Part I Cohort A), freshly collected biopsies (baseline and on-treatment) are optional.

For all other participants, fresh tumor biopsies (i.e., one *mandatory* at baseline; once eligibility has been confirmed, exception Cohort E as stated below, and one *optional* on treatment) will be collected. For participants in Part I Cohort D, gemcitabine or vinorelbine control arm only, on-treatment biopsies are optional.

For Cohort E if archival tissue is not available, a fresh biopsy will be required to determine PD-L1 status for eligibility. In addition, recent historic PD-L1 results from Ventana SP263 or Dako 22C3 IVD/CE tests can also be utilized. This biopsy sample will also be used as the baseline biopsy if the participant is enrolled (i.e., a repeat biopsy is not necessary). At Baseline, the fresh tumor biopsy will only be taken once all other inclusion/exclusion criteria have been met. PD-L1 assessment will be performed on the archival and/or fresh tumor biopsy.

Additional optional on-treatment fresh tumor biopsies of progressing and/or regressing lesions might be collected in any participant, at the Investigator's discretion, to characterize the participant's response to treatment.

Collection of tumor biopsies should be guided by ultrasound, CT scan, or other methods according to the location of the selected lesion by using preferably a 16-gauge needle to provide cores, ideally, of at least 20 mm in length or equivalent size. At least two cores per biopsy timepoint are to be collected. Cytological, fine needle aspirations (including endobronchial ultrasound [EBUS]), or biopsies of bone lesions are not acceptable. For study part III only, surgical (incisional or endoscopic) specimens are acceptable, if an adequate amount of material can be safely obtained (ideally a minimum of 44 mm^3 per scheduled timepoint).

Please see the Laboratory Flow Chart document for biopsy sample collection procedures.

The baseline and on-treatment biopsies should preferably be taken from the same tumor lesion (metastasis) to ensure comparability. If the lesion biopsied at baseline cannot be biopsied on-treatment (i.e., lesion is no longer present) then an alternative lesion should be biopsied. Preferably, the new lesion would be in a similar tissue. The location of each biopsy will be documented in relation to each tumor lesion, as determined by imaging. If the participant progresses and discontinues treatment before 6 weeks of treatment, the tumor biopsy should be taken at the time of treatment discontinuation. If feasible, on-treatment biopsies may be repeated if the initial biopsy did not contain sufficient tumor material for analysis. If preliminary data suggest, alternative on-treatment tumor biopsy timepoints may be considered upon joint agreement between Investigators and the Sponsor.

An additional biopsy at the time of disease progression, PR, SD, or at any other timepoint of interest based on participants' course of disease may be taken after discussion between the Investigator and the Sponsor.

Available existing biopsies at the sites before the participant's entry in the study should be discussed with the Sponsor (i.e., biopsy should have recently been obtained as part of diagnosis biopsy and participants should have not received any tumor treatment after this collection).

The residual tissue material (slides, extracts, etc.), PD whole blood, serum, plasma, and clinical genotyping samples will be destroyed within 2 years after the date of final clinical study report (CSR), unless the participant gives specific consent for the remainder of the residual tissue material, PD serum, PD plasma, and clinical genotyping sample(s) to be stored for potential exploratory research within the RBR. If the participant provides consent for potential exploratory research, the samples will be destroyed no later than 15 years after the date of final CSR.

In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the fixed and embedded biopsy (FFPE block) can be returned to the site upon site request.

Any residual material may be used for additional as well as exploratory biomarker profiling, identification, assay development purposes, and assay validation during the development of study or compound-related assays after the mentioned intended uses.

Contingent upon the confirmation of the treatment's safety and preliminary activity analysis, a mandatory biopsy cohort (Part I Cohort C) may be introduced to enroll CPI-naïve NSCLC participants. This will include 20 participants and will follow the same sample collection and analysis plan as these described for the CPI-experienced NSCLC participants above.

8.7 GENETICS

8.7.1 Clinical Genotyping

A mandatory whole blood sample for DNA analysis will be taken once, at baseline or before study treatment administration (see Section 1.3). If this sample is missed, it can be collected at any other scheduled visit. The DNA will be used to determine if alleles at genes associated with immunity, such as KIR and HLA, affect the PK, PD, activity, or safety of the study treatment. This may include genome sequencing, to investigate biomarkers that might predispose the participant for drug-associated autoimmunity or to a positive tumor response to the study treatments combination. These assessments will be performed if safety or activity rationales develop.

The residual tissue material (including whole blood) will be destroyed within 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of

the residual tissue material to be stored for potential exploratory research within the RBR. If the participant provides consent for potential exploratory research, the samples will be destroyed no later than 15 years after the date of final CSR.

Details on processes for collection and shipment of these samples can be found in Sample Handling Manual.

8.7.2 Whole Genome/Exome/Targeted DNA Analysis

Archival or fresh tumor tissue sample and plasma sample will be collected at baseline for DNA and/or RNA extraction (see Section 1.3) for exploratory research on genetic biomarkers (may include, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways, or immune-related markers, microsatellite instability, and tumor mutation burden).

Any remaining tissue after the specified analyses may also be used for additional (assay) validation experiments.

These samples will be destroyed no later than 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of the residual tissue material to be stored for potential exploratory research within the RBR. If the participant provides consent for potential exploratory research, the samples will be destroyed no later than 15 years after the date of the final CSR.

8.7.2.1 Transcriptome Analysis

Tissue biopsies will be collected (see SoAs, Section 1.3) for RNA extraction as described above and subsequent gene expression profiling to enable:

- Identification of PD biomarkers.
- Identification of response predictive biomarker.
- Assessment of treatment response (PD).

Any remaining tissue after the specified analyses may also be used for additional (assay) validation experiments.

These samples will be destroyed no later than 2 years after the date of final CSR, unless the participant gives specific consent for the remainder of the residual tissue material to be stored for potential exploratory research within the RBR. If the participant provides consent for potential exploratory research, the samples will be destroyed no later than 15 years after the date of final CSR.

8.8 BIOMARKERS

For description of biomarker analyses, please refer to Section 8.6 and Section 8.7.

8.8.1 Samples for Research Biosample Repository

8.8.1.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Residual samples from participants who give specific consent to participate in this optional RBR will be stored. Stored specimens will be used to achieve the following objectives:

- To study the association of biomarkers with activity, AEs, or progressive disease.
- To increase knowledge and understanding of disease biology.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

8.8.1.2 Sample Collection

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

- Residual plasma samples
- Residual serum samples
- Residual fresh tissue samples
- Residual whole blood samples
- Residual samples prepared from whole blood and tissue samples (e.g., DNA, RNA)
- Residual samples from additional safety monitoring, if applicable

The sample collected for DNA extraction include, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing, whole exome sequencing, next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability

of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

RBR specimens will be stored and used no later than 15 years after the date of the final CSR. The RBR storage period will be in accordance with the EC/IRB-approved ICF and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

8.9 HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

8.10 TIMING OF STUDY ASSESSMENTS

All assessments must be performed as per SoAs (see Section 1.3).

8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. The screening window clock starts with the first study-specific screening test or evaluation and not the consent date. ICFs for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

8.10.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified, be permitted to re-enroll in the study.

8.10.3 Assessments at Study Completion/Discontinuation Visit

Participants who complete the study or discontinue from the study early will be asked to return to the clinic 28 days after the last dose of study treatment for a follow-up visit. The

visit at which response assessment shows progressive disease may be used as the study completion/discontinuation visit.

8.10.4 Follow-Up Assessments

Participants will be treated with study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Participants may continue study treatment for a maximum of *24* months.

As with other immunotherapies, treatment beyond RECIST progression could be considered after approval of the Sponsor. The criteria needed for continuing treatment beyond initial apparent progressive disease per RECIST v1.1 (e.g., radiological progression secondary to tumor inflammation) are outlined in Section 7.2.

Post-study Survival Follow-up:

The sites will provide to the Sponsor every 3 months (starting at Day 120 visit ± 30 days) an update on survival status of each of the participants enrolled in the study for approximately 36 months after LPLV. The sites will use a designated section of the eCRF for this purpose.

After the study completion/discontinuation visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

All assessments must be performed as per SoAs (see Section 1.3).

8.10.5 Assessments at Unscheduled Visits

Please see Section 1.3 for activities that are required to be performed in case of an unscheduled visit.

9. STATISTICAL CONSIDERATIONS

The data will be analyzed by the Sponsor and/or designated contract research organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, activity observations and measurements, safety observations and measurements, and PK and biomarker measurements. Data will be reported by part and by cohort/arm separately.

9.1 STATISTICAL HYPOTHESES

In Part I, Cohort D, the hypothesis of superiority of the treatment of *simlukafusp alfa* in combination with atezolizumab over gemcitabine or vinorelbine in participants with advanced and metastatic NSCLC, who experienced progressive disease after or during docetaxel therapy and on or after CPI therapy, will be tested.

The hypothesis will be tested separately for each schedule of administration.

For all cohorts, except Cohort D, no formal hypothesis will be tested.

9.2 SAMPLE SIZE DETERMINATION

In Part I, which focuses on participants with advanced and/or metastatic NSCLC, 110 response-evaluable participants will be enrolled, with 20 participants in each cohort (i.e., Cohorts A, B, and C). In Cohort D, 120 participants were to be randomized to each schedule of the combination or to the control arm. The cohort is now closed with an enrollment of 10 participants. Cohort F will include 40 response-evaluable participants.

In Cohort C, which will enroll participants with NSCLC who are CPI-naïve, biopsies are mandatory. This cohort may be opened in Part I or other parts on the basis of emerging data and may include up to 20 response-evaluable participants.

In Part II Cohort E, which focuses on participants with previously untreated advanced and/or metastatic NSCLC, 40 response-evaluable participants were to be randomized to each schedule of the combination. The cohort is now closed with an enrollment of up to 10 participants.

In Part III, Cohorts G, H, I, J, K, L, M, and N will enroll 20 participants each. In any of these cohorts, the sample size may be extended to a total of 80 participants per cohort.

Other parts, focusing on other tumor types may be opened on the basis of emerging data from this study and other studies.

The total sample size for this study will initially be up to 280 response-evaluable participants (not including the possible extensions of Part III). To compensate for the loss of participants that are not response-evaluable, or participants for whom the required biopsy is not available, the recruitment in the cohorts may be increased.

Additional participants may be enrolled in the event that less than 60% of paired fresh baseline and on-treatment biopsies are evaluable to conclude the Pharmacodynamic Biomarker analyses. Further, additional participants also may be enrolled in case archival tissue samples are provided for less than 80% of all participants.

9.2.1 Sample Size Justification for Part I

For the CPI-naïve Cohort A, the sample size of 20 response-evaluable participants allows to declare futility with 80% chance under the assumption that the true ORR is 10%, based on the posterior probability for ORR to be below 20% with a 70% confidence level. Futility will be assessed after 10 participants have mature data. Futility will be concluded if less than 2 out of 10 participants or less than 3 out of 20 participants have CR or PR.

For the CPI-experienced Cohort B, the sample size of 20 response-evaluable participants allows to declare futility with 78% chances under the assumption that the

true ORR is 5%, based on the posterior probability for ORR to be below 10% with a 70% confidence level. Futility will be assessed after the first 10 participants have mature data. Futility will be concluded if less than 1 out of 10 participants or less than 2 out of 20 participants have CR or PR.

For Cohort D: The hypothesis of superiority of the combination of *simlukafusp alfa* in combination with atezolizumab over gemcitabine or vinorelbine will be tested on the primary endpoint of ORR using a normal approximation for the difference of proportion (Farrington & Manning 1990).

The hypothesis testing will be controlled at an overall alpha level of 0.2. This alpha level will be equally split between the comparison of the Q3W arm versus the control and the QW/Q2W arm versus the control. The total sample size for Cohort D will be 120 participants allocated in a 2:2:1 ratio. The sample size of 24 participants in the control arm and 48 participants in each experimental arm will allow detection of a 23% difference with 80% power under the assumption of control treatment ORR of 5% at an alpha level of 0.1 for each comparison.

Futility will be assessed after the enrollment of 20 participants in each experimental arm and 10 participants in the control. Futility will be declared if less than 1 responder out of 20 participants is observed in the experimental arms. This will ensure that arm will be stopped with more than 80% chance if the combination treatment is not efficacious (i.e., assuming a true ORR = 0%). Futility rules will be non-binding.

For the CPI-experienced, platinum-experienced, docetaxel-naïve Cohort F, the sample size of 40 response-evaluable participants allows to declare futility with 91% chance under the assumption that the true ORR is 5%, based on the posterior probability for ORR to be below 10% with a 70% confidence level. Futility will be assessed after the first 20, 30, and 40 participants have mature data. Futility will be concluded if less than 2 out of 20 participants, less than 3 out of 30 participants or less than 4 out of 40 participants have CR or PR.

9.2.2 Sample Size Justification for Part II

For Cohort E, in each arm, the sample size of 40 response-evaluable participants allows to declare futility with 86% chances under the assumption that the true ORR is 30%, based on the posterior probability for ORR to be below 44.8% with a 90% confidence level. The futility level of 44.8% is based on the pembrolizumab data. Futility will be assessed after the 20, 30, and 40 participants have mature data. Futility will be concluded if 6 or less out of 20 participants, or 11 or less out of 30 participants, or 13 or less out of 40 participants have CR or PR.

9.2.3 Sample Size Justification for Part III

In Cohorts G, H, I, J, K, L, M, and N, the sample size of 20 response-evaluable participants allows the declaration of futility with 78% chance under the assumption that

the true ORR is 5%, based on the posterior probability for ORR to be below 10% with a 70% confidence level. Futility will be assessed after the first 10 participants have mature data. Futility will be concluded if less than 1 out of 10 participants or less than 2 out of 20 participants have CR or PR.

For any of these cohorts, the sample size may be extended to 80 participants in total to allow a robust estimation of the efficacy of the *simlukafusp alfa* in combination with atezolizumab. The cohort may be extended only after the futility is rejected. The total sample size will allow the estimation of ORR with a maximum width of the exact 95% CI of 23%.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 18.

Table 18 Analysis Populations

Population	Description
Response evaluable	All participants in the safety population who received at least one dose of *simlukafusp alfa*/atezolizumab and who have at least one baseline and one on-study tumor assessment. Participants who received at least one dose of *simlukafusp alfa*/atezolizumab and discontinued the study because of progression before the first on-study tumor assessment will be considered as response-evaluable.
Intend to treat population (ITT)	All participants randomized in the Part I Cohort D.
Safety	All participants who received at least one dose of study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made before database closure.
Immunogenicity	All participants who had at least one pre-dose and one post-dose ADA assessment will be included and analyzed according to the treatment they actually received.
Pharmacodynamic	All participants who had at least one pre-dose and one post-dose PD assessment will be included and analyzed according to the treatment they actually received.

Abbreviations: ADA = anti-drug antibodies; ITT = intent to treat; PD = pharmacodynamic; PK = pharmacokinetic.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

The study population will be described by demographic characteristics (including age, sex, participant disposition, and previous therapies). Treatment administration will be reported on the basis of number of cycles and dose intensity. The analysis will be based on the safety analysis population and on the intent−to-treat (ITT) population by arm as randomized (Part I Cohort D)

9.4.2 Activity Analyses

ORR and disease control rate (DCR) are determined as the rate of participants with an observed tumor response of CR or PR (ORR) or CR, PR, or SD (DCR). To classify a response as SD, measurements will have to be classified as stable (according to RECIST v1.1) at least once after study entry at a minimum of 6 weeks after study entry. Participants with missing or no response assessments will be classified as not evaluable for activity unless there is documented clinical deterioration, in which case the participant will be classified as non-responders.

Duration of response (DoR) will be calculated for participants who have a best overall response of CR or PR and will be defined as the time from first occurrence of a documented objective response until the time of documented disease progression or death from any cause during treatment, whichever occurs first. Censoring methods will be the same as the one applied for PFS.

PFS will be defined as the time from study treatment initiation (Cycle 1 Day 1) to the first occurrence of documented disease progression (based on Investigator's assessment) or death from any cause during treatment, whichever occurs first. For participants who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment.

OS is defined as the time from the first dose of study treatment to the time of death from any cause on study. Participants who are still alive at the time of analysis will be censored at the time of their last study assessment (for active participants) or at the last date known alive (for participants in follow-up).

9.4.2.1 Part I Cohorts A, B, C, and F; Part II Cohort E; and Part III Cohorts G, H, I, J, K, L, M, and N

The primary and secondary activity analyses will include all participants in the response-evaluable population. No formal statistical model and no formal hypothesis testing are planned in this study. The statistical analysis methods for activity are presented in Table 19.

Table 19 Activity Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary: ORR	ORR will be tabulated along with 95% exact CI.
Secondary:	
DCR	DCR rate will be tabulated along with its 95% exact CI.
DoR, PFS, and OS	DoR, PFS, and OS (if data are mature) will be summarized using the Kaplan-Maier estimator for time-to-event endpoints. Median and 95% Clopper-Pearson CI will be provided. The figure of the distribution will be provided.
Exploratory	An assessment of TGK will be made by comparing post-treatment scans with the baseline scan using longitudinal analysis.

Abbreviations: CI = confidence interval; DCR = disease control rate; DoR = duration of response; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; TGK = tumor growth kinetic.

The primary analyses of response endpoints will be conducted using the RECIST v1.1 criteria based on the investigator assessments. Classification of PR and CR will be based on confirmed assessments. Sensitivity analyses may include the evaluation of response according to iRECIST and the evaluation of response from an independent centralized review (ICR).

For the tumor growth kinetic model, data may be explored by linear and/or exponential models, as appropriate, in non-linear mixed effect modeling software. The analysis will be conducted if the data collected allow the fit of these models.

The evaluation of the activity of the treatment combination relative to the standard of care will be initially performed through an informal comparison against historical data.

9.4.2.2 Part I Cohort D

The superiority of *simlukafusp alfa* in combination with atezolizumab over gemcitabine or vinorelbine (control) will be tested. Two separate hypotheses will be tested: superiority of Q3W versus control and superiority of QW/Q2W versus control. The tests will be conducted on the ITT population by arm as randomized. The overall type I error of 0.2 will be split equally on each hypothesis. The primary endpoint for the comparison will be ORR and the secondary endpoints will be tested hierarchically at an alpha level of 0.1 (see Table 20 for ordering). One interim analysis for futility will be conducted for each hypothesis when 10 and 20 participants will be enrolled in the control and experimental arms respectively. At this interim, the superiority will be tested at an alpha level of 0.00001 to preserve the alpha level of the final analysis. The analyses will be conducted on the ITT population.

Table 20 Part I Cohort D: Activity Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary: ORR	Difference in ORR will be tested using a normal approximation for the difference of proportion (Farrington 1990). Difference between arms will be tabulated along with the 95% CI (computed from the normal approximation for consistency with the test). ORR will be tabulated along with its 95% exact CI.
Secondary (in order of testing):	
PFS	Difference in PFS will be tested using an unstratified logrank test. Hazard ratio will be provided along with its 95% CI. PFS will be summarized using the Kaplan-Maier estimator for time-to-event endpoints. Median and 95% Clopper-Pearson CI will be provided. The figure of the distribution will be provided.
DCR	DCR will be analyzed using the same methods as ORR
Secondary (no comparison):	
DoR	DoR will be summarized using the Kaplan-Maier estimator for time-to-event endpoints. Median and 95% Clopper-Pearson CI will be provided. The figure of the distribution will be provided.
Exploratory	An assessment of TGK will be made by comparing post-treatment scans with the baseline scan using longitudinal analysis.

Abbreviations: CI=confidence interval; DCR=disease control rate; DoR=duration of response; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; TGK=tumor growth kinetic.

The primary analyses will be conducted on the RECIST v1.1 response/progression evaluated by the investigator. Classification of PR and CR will be based on confirmed assessments. Sensitivity analyses using the IRC assessments and iRECIST criteria will be conducted.

Stratification: Given the small number of participants in the control group and the risk of having a stratum that is too small, the analyses will not be stratified. A sensitivity of the primary and secondary endpoint testing will be conducted using a Cochran-Mantel-Haenszel (CMH; for binary endpoints) and a stratified logrank test (for PFS). The stratification factor will be the one used for randomization (using data collected at the time of randomization).

OS: Given that participants are allowed to crossover to one of the experimental arms, OS will not be analyzed for Cohort D.

For the tumor growth kinetic model, data may be explored by linear and/or exponential models, as appropriate, in non-linear mixed effect modeling software. The analysis will be conducted if the data collected allow the fit of these models.

9.4.3 Safety Analyses

All safety analyses will be based on the safety population and by arm as treated (Part I Cohort D). The statistical analysis methods for safety are presented in Table 21.

Table 21 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
AEs	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level. Individual participant listings will be produced.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results. Shifts in NCI CTCAE v4.03 grades from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. Individual participant listings will be produced. See Appendix 4 for details on standard reference ranges and data transformation and the definition of laboratory abnormalities.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate. Individual participant listings will be produced.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms. Concomitant medications will be presented in summary tables and listings.

Abbreviations: AE = adverse event; ECG = electrocardiogram; eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

9.4.4 Pharmacokinetic Analyses

Simlukafusp alfa and atezolizumab serum concentrations will be measured by a validated enzyme-linked, immunosorbent assay (ELISA) method.

PK sampling will be performed in this study to properly characterize the PK of *simlukafusp alfa*. When appropriate, PK parameters will be derived from the serum concentrations of *simlukafusp alfa* using standard non-compartmental methods.

Individual and mean serum *simlukafusp alfa* and atezolizumab concentration versus time data will be tabulated and plotted by dosage-levels and/or dosing regimens. All PK parameters will be presented by listings and descriptive summary statistics separately by dosage-levels and/or dosing regimens.

Parameters may include, for example, AUC, clearance, and volume of distribution under steady-state conditions, as appropriate. These parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-participant variability and drug accumulation will be evaluated.

Non-linear mixed effect modeling will be used to analyze the samples of concentration–time data of *simlukafusp alfa* and atezolizumab. For *simlukafusp alfa*, population and individual PK parameters will be estimated, and the influence of various covariates (such as age, gender, and body weight) on these parameters will be investigated in an exploratory way. A previously developed model for atezolizumab PK will be used to provide individual parameter estimates using Bayesian feedback methodology. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively. Additionally, exploratory analyses on exposure and safety/activity relationship may be conducted if deemed necessary. The details of the modeling and exploratory analyses will be reported in a document separate from the CSR.

9.4.5 Pharmacodynamic Analyses

The following PD parameters will be presented by listings and descriptive summary statistics separately by group or cohorts.

- PD-L1 status
- Change from baseline in density (cell/mm2) of CD8+ and CD3-perforin+ cells, and PD-L1.

Depending on findings, other PD parameters may be presented by listings and descriptive statistics as appropriate.

9.4.6 Other Analyses

Graphical or exploratory analyses may be performed to assess the possible relationship between exposure to *simlukafusp alfa* and selected biomarkers, activity, or safety parameters as appropriate.

9.5 INTERIM ANALYSES

In Part I Cohorts A and B and Part III Cohorts G, H, I, J, K, L, M, and N, activity (ORR) will be evaluated in one interim analysis in each cohort. This interim analysis will take place when 10 participants have a mature assessment of response in each cohort.

In Part I Cohort F and Part II Cohort E, an interim analysis of ORR will be conducted in each arm after the first 20 and 30 participants have mature assessments.

In Part I Cohort D, one futility interim analysis will be conducted on the data from the first 10 and 20 participants (in the control arm and in each experimental arm, respectively) who have mature data.

Recruitment may not be interrupted while waiting for data maturity.

These futility rules are not binding and may be overruled if other endpoints (e.g., DCR rate, DoR, PFS, or OS) show significant improvement over the expected benefit in the population.

At any time during the study, parts, cohorts, and arms may be closed based emerging data external to the study or operational reasons.

9.6 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes the following appendices:

Appendix 1 for regulatory, ethical and study oversight considerations.

Appendix 2 for AE definitions, reporting.

Appendix 3 for procedures for recording AEs.

Appendix 4 for clinical laboratory tests.

Appendix 5 for contraceptive guidance and collection of pregnancy information.

Appendix 6 for Cockcroft-Gault formula.

Appendix 7 for revised RECIST guideline version 1.1.

Appendix 8 for modified RECIST version 1.1.

Appendix 9 for management guidelines for atezolizumab.

Appendix 10 for ASTCT grading.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a US Investigational New Drug application will comply with US Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union/ European Economic Area will comply with the European Union Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the informed consent forms (ICFs), any information to be given to the participant (e.g., advertisements, diaries), and relevant supporting information must be submitted to the institutional review board (IRB)/ethics committee (EC) by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant 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 (Section 2.3.1 of this appendix).

The Investigator should follow the requirements for reporting all AEs to the Sponsor. Investigators may receive written investigational new drug 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.

1.3. INFORMED CONSENT

The Sponsor's master ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's 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. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act requirements, where applicable, and the IRB/independent EC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant’s legally authorized representative before his or her 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 before 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 participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant 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 participant’s study file or in the site file and must be available for verification by study monitors at any time.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the Research Biosample Repository (RBR). The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant’s agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR page of the electronic case report form (eCRF).

In the event of death or loss of competence of a participant who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

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

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant’s wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study BP40234 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP40234. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Confidentiality for Research Biosample Repository

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR specimen analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

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

Monitoring and Oversight Research Biosample Repository

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

1.5. 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 one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.3. Source Data Records

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, clinical outcome assessments (paper or electronic clinical outcome assessments), 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 trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no previous written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

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 below.

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

2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational 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.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the EC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval before submission. This allows the Sponsor to protect proprietary information and to provide comments on the basis of information from other studies that may not yet be available to the Investigator.

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

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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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.

2.3.3. 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.

3. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or 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 AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the EC/IRB or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow Up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** (AE) is any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- 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.

Events Meeting the AE Definition:

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., electrocardiogram, x-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur before assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of activity" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the activity assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of activity will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., electrocardiogram, x-ray) that is NOT associated with symptoms and does NOT lead to a change in study treatment or concomitant treatment or discontinuation from study treatment.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious AE (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - Disability means substantial disruption of the participant's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**
- **Other significant events**:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the electronic case report form (eCRF).

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor and/or Medical Monitor.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to a predefined grading criteria [eg, NCI CTCAE criteria); 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 AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 1 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale

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 AE [d]

AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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 one's self, 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 AE (SAE) (see Section 6 of this appendix for reporting instructions), per the definition of SAE in Section 2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 6 for reporting instructions), per the definition of SAE in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meet one or more of the conditions outlined in Section 2. See Section 1 for the definition of AEs.

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment.

- Known association of the event with the 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.

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

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, from a related AE and the autopsy is available, the Investigator will provide the Sponsor with a copy of any postmortem findings.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- SAEs
- Non-serious AEs of special interest
- Pregnancies (see Section 8.3.5)
- Accidental overdoses or medication errors (see Appendix 2, Section 5.2 for details on reporting requirements)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

Investigators must also comply with local requirements for reporting SAEs to the local Health Authority and institutional review board/ethics committee.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events That Occur Before Study Treatment Initiation

After informed consent has been obtained, but before initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events That Occur After Study Treatment Initiation

For reports of SAEs and non-serious AEs of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

After the end of the AE reporting period (see Section 8.3.1) after the last dose of study treatment), 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 an SAE that is believed to be related to previous study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to Investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
- In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with *simlukafusp alfa* in combination with Atezolizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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.
- For all study drugs, 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, the event should be reported to the Sponsor

immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). For *simlukafusp alfa* in combination with Atezolizumab, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, institutional review boards, ethics committees, and applicable Health Authorities based on applicable legislation.

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

- *Simlukafusp Alfa* Investigator's Brochure/Atezolizumab Investigator's Brochure
- Gemcitabine and vinorelbine: UK SmPC

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

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

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events (AEs) on the AE electronic case report form (eCRF). Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the AE eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. INFUSION/ INJECTION-RELATED REACTIONS

AEs that occur during or within 24 hours after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the AE eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the AE eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

1.2. OTHER ADVERSE EVENTS

For AEs other than infusion-related reactions, a diagnosis (if known) should be recorded on the AE 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 AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring 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. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the AE 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 subsequent fracture, all 3 events should be reported separately on the eCRF.

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

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

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

- 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.
- Clinically significant in the Investigator's judgment.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be

characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the cause changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

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

- 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.
- Clinically significant in the Investigator's judgment.

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the cause changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

For participants without liver metastases, the finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN.
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice.
- ALT $\geq 3\times$ ULN and international normalized ratio >1.5.

For oncology participants who have liver metastases or hepatocellular carcinoma or are receiving hepatotoxic concomitant medications, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>$ 5 $\times$ ULN value in combination with total bilirubin $>$ 2 $\times$ ULN (of which $\geq$ 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>$ 5 $\times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 8.2.8) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious AE (SAE) or a non-serious AE of special interest (see Section 8.3.6).

7. OVERDOSE

See Appendix 2.

8. DEATHS

For this protocol, mortality is an activity endpoint. Deaths that occur during the protocol-specified AE reporting period (see Appendix 2, Section 5) that are attributed by the Investigator solely to progression of advanced and/or metastatic solid tumors should be recorded only on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the AE eCRF and immediately reported to the Sponsor (see Appendix 2, Section 5).

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 AE 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 AE 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").

9. PREEXISTING MEDICAL CONDITIONS

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

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the preexisting

condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10. LACK OF ACTIVITY OR WORSENING OF ADVANCED AND/OR METASTATIC SOLID TUMORS

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as activity assessment data only. In most cases, the expected pattern of progression will be based on criteria (e.g., Response Evaluation Criteria in Solid Tumors). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to progressive disease, it should be reported as an AE.

11. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned before 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 suffered an AE.
- Hospitalization due solely to progression of the underlying cancer

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

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

12. PARTICIPANT-REPORTED OUTCOME DATA (CLINICAL OUTCOME ASSESSMENTS DATA REPORTED DIRECTLY BY PARTICIPANT)

AE reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data. Roche/Genentech study team will determine whether any PRO data elements may be indicative of a medically significant AE (e.g., suicidal ideation, worsening of depression, worsening of hemoptysis) and could necessitate real time review by the site or Sponsor.

Appendix 4
Clinical Laboratory Tests

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH, CRCL (by Cockcroft-Gault formula, Appendix 6), GGT, Magnesium, CRP, ferritin, troponin I/T (either troponin I or T can be performed, but it must be consistent for each participant).
Coagulation	INR, aPTT, PT. If clinically indicated, anti-thrombin III, fibrinogen, fibrin degradation products, D-dimer should be analyzed.
Viral Serology	HIV (specific tests HIV-1 antibody, HIV-1/2 antibody), HIV-2 antibody), hepatitis A IgM antibody, hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus antibody, hepatitis E IgM antibody
Lipids	Cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
Thyroid Hormones	TSH (Free T3 and Free T4 should be performed only if TSH is abnormal)
Pregnancy Test	All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at specified timepoints. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A pregnancy test will also be performed at the 120-day after last dose of atezolizumab follow-up visit. Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase If there is a clinically significant *hematuria* (confirmed by a positive repeated sample *and in the absence of an explanation, e.g. menses*), urine will be sent to the laboratory for microscopy. *Culture and sensitivity analysis is indicated if urinary tract infection is suspected.* • Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).
Autoantibodies	• Anti-nuclear antibody, anti−double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody (cANCA), and perinuclear anti-neutrophil cytoplasmic antibody (p ANCA)
In Case of Suspected IRR (only)	IgE, tryptase

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRCL = creatinine clearance; CRP = c-reactive protein; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PT = prothrombin time; TSH = thyroid-stimulating hormone.

For specified timepoints, see Table 1, Table 2, and Table 3 for the Part I and Part II Q2W schedule, Table 4, Table 5, and Table 6 for the Part I and Part II Q3W schedule, and Table 7 for the Part I Best Standard of Care (Cohort D Control Arm) schedule.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges (e.g., enzyme tests that include AST, ALT, alkaline phosphatase, and total bilirubin). Because the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile after menarche and until becoming post-menopausal unless permanently sterile.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] (Failure rate of < 1% per year when used consistently and correctly)
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Abbreviations: WOCBP = woman of child-bearing potential.

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5). This applies only to male participants who receive study treatment.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- **Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE electronic case report form (eCRF), any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered

reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as a serious adverse event, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or 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 8.3).

Appendix 6
Cockcroft−Gault Formula for Calculation of Creatinine Clearance

Creatinine Clearance (ml/min) for males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)}$$

Creatinine Clearance (ml/min) for Females:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age } \langle\text{years}\rangle \times \text{body weight } \langle\text{kg}\rangle)}{(72) \times (\text{serum creatinine } \langle\text{mg/dL}\rangle)} \times 0.85$$

Appendix 7
New Response Evaluation Criteria in Solid Tumors – Version 1.1 – Modified Excerpt from Original Publication with Addition of Supplementary Explanations [1]

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also Section 2.2 on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable Tumor Lesions

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

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with previous local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

1.2.1 Measurement of Lesions

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

1.2.2 Method of Assessment

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

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

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If before enrollment it is known that a participant is unable to undergo CT scans with intravenous contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without intravenous contrast) will be used to evaluate the participant at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the previous studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the participant should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised but will be dependent on the study design.

2.2.2 TUMOR RESPONSE EVALUATION

2.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1).

2.2. BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where participants have only one or 2 organ sites involved a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is ≥10 mm by CT scan).

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

Lymph nodes merit special mention because they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

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

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

of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4. Special Notes on Assessment of Progression of Non-target Disease

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

When the participant has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the participant should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be **substantial**.

2.3.5. New Lesions

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

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

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

2.4 EVALUATION OF RESPONSE

2.4.1 Time-Point Response (Overall response)

It is assumed that at each protocol specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for participants who have measurable disease at baseline.

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

Table 1 Time-Point Response – Target (w/wo non-target) Lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Abbreviations: w/wo = with or without.

Table 2 Time-Point Response – Non-Target Lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the participant is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of progressive disease.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved progressive disease status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" because the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that timepoint.

Table 3 Best Overall Response when Confirmation is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted

earlier, this means that participants with CR may not have a total sum of 'zero' on the case report form (CRF).

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

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

In studies where participants with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.

Appendix 8
Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) have been developed to allow for unconventional response and progression patterns. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions

EVALUATION OF LESIONS TO SUPPORT iRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to $<$15 mm (or even $<$10 mm).

Table 1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Abbreviations: CR = complete response; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.

Hodi FS, Ballinger M, Lyons B, et al. Immune-modified Response Evaluation Criteria In Solid Tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol 2018;36(9):850–858.

Seymour L, Bogaerts J, Perrone A, et al. On behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143– e152.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–7420.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

The text in this appendix is taken from the Atezolizumab Investigator's Brochure, Version 17. However, please refer to the current version of the Atezolizumab Investigator's Brochure for the latest safety information.

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-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit–risk balance *for* a given participant prior to further administration of atezolizumab. In participants who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the participant is deriving benefit and has fully recovered from the immune-related event. Participants can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for $>$12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. 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 participant referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • 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 Medical Monitor.[c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Bronchoscopy or BAL is recommended. • 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.

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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab. Participants *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.

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

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. 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 3 to 5 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. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
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 resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-related event. Participants can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Participants 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. Participants should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider participant referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold 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. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism. [c]

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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. • Participant 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] • Participant 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 Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any participant 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. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All participants 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.

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

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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 event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related myocarditis, Grade 3 *or* 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD 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.

[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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, 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 COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, 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 COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 **Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome**

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, 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 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, anti-pyretics, 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 Medical Monitor.

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

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact 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 NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE 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, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal; ULN = upper limit of normal.

[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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related 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 Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact 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; IV = intravenous.

[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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

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

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider participant 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.
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 Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	*Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:* • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis, 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 agreed upon by the investigator and the Medical Monitor.*

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact 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.

IV = intravenous.

[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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related 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 participants 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 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact 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.

IV = intravenous.

[a] Resumption of atezolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-related event. Participants can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, 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 Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-RELATED MYOSITIS

Immune-related myositis has been associated with the administration of atezolizumab. 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 signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 13 Management Guidelines for Immune-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-related myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

[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 agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 13 Management Guidelines for Immune-Related Myositis (cont.)

Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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), *which are considered to be potential risks for atezolizumab.*

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

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

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
- Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)

- Fasting triglycerides $>$2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq$ 181 $\times$ 109/L (181,000/μL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact 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 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 $\geq$ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 10 ASTCT Cytokine Release Syndrome Consensus Grading (Lee et al 2019)

CRS grade[a]	*Clinical Parameter:*				
	Fever[b]		*Hypotension*		*Hypoxia*
Grade 1	*Temperature ≥38°C*	*with*	*None*	*and/ or*[c]	*None*
Grade 2	*Temperature ≥38°C*		*Not requiring vasopressors*		*Requiring low-flow nasal cannula*[d] *or blow-by*
Grade 3	*Temperature ≥38°C*		*Requiring a vasopressor with or without vasopressin*		*Requiring high-flow nasal cannula, facemask, nonrebreather mask or Venturi mask*
Grade 4	*Temperature ≥38°C*		*Requiring multiple vasopressors (excluding vasopressin)*		*Requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)*

Abbreviations: CRS: Cytokine Release Syndrome; ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure.

[a] CRS grading per ASTCT (Lee et al. 2019).
[b] Fever is defined as temperature ≥38°C, not attributable to any other cause. In patients who develop CRS, and then receive antipyretic or anti-cytokine therapy (e.g. tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[c] CRS grade is determined by the more severe event: hypotension or hypoxia, not attributable to any other cause.
[d] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.