PROTOCOL

TITLE:	**A PHASE Ib, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) ADMINISTERED IN COMBINATION WITH Hu5F9-G4 TO PATIENTS WITH RELAPSED AND/OR REFRACTORY ACUTE MYELOID LEUKEMIA**
PROTOCOL NUMBER:	GO40828
VERSION NUMBER:	3
EUDRACT NUMBER:	Not applicable
IND NUMBER:	*147530*
NCT NUMBER:	NCT03922477
TEST PRODUCTS:	Atezolizumab (RO5541267) and Hu5F9-G4
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
05-Aug-2020 23:24:57	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	5 February 2020
1	13 December 2018

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol GO40828 has been amended in response to feedback from the U.S. Food and Drug Administration (FDA) Division of Hematologic Malignancies 1 (DHM1). Changes to the protocol are summarized below:

- Rules for dose modification and changes in dose scheduling following dose-limiting toxicity (DLT) have been amended for clarity and consistency with the study design (Sections 3.1.1 and 3.1.2.2).
- Language has been added regarding suggested testing for the determination of the underlying etiology and appropriate attribution for DLTs (Section 3.1.2.3).
- DLT definitions have been modified to address specific concerns outlined by the FDA (Section 3.1.2.3).
- A stopping rule for excess toxicity for the expansion phase has been added, including clinical assumptions and description of the statistical methodology used to calculate the early stopping bounds (Section 3.1.2.4, Table 1).
- The projected enrollment period and length of study have been updated (Section 3.2).
- Language has been added to provide additional rationale for the atezolizumab starting dose and schedule in this population (Section 3.3.1).
- The inclusion criteria have been revised to include only patients with relapsed and/or refractory acute myeloid leukemia who have experienced treatment failure with all therapies of known benefit (Section 4.1.1).
- Management guidelines for infusion-related reactions have been revised to incorporate observation periods between atezolizumab and Hu5F9-G4 infusions on days when both drugs are administered (Section 4.3.2 1, Table 2 and Appendix 1).
- The IND number has been replaced throughout the protocol with a new IND number assigned by the DHM1.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

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PHASE:	Ib
INDICATION:	Acute myeloid leukemia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This Phase Ib study is designed to evaluate the safety and pharmacokinetics of atezolizumab when given in combination with Hu5F9-G4 to patients with relapsed or refractory (R/R) acute myeloid leukemia (AML). Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab and Hu5F9-G4).

Safety Objective

The primary safety objective for this study is to characterize the safety and tolerability of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- Incidence of adverse events, with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Change from baseline in physical examination findings

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab and Hu5F9-G4 when administered in combination to patients with R/R AML on the basis of the following endpoints:

- Serum concentrations of atezolizumab
- Serum concentrations of Hu5F9-G4 at specified timepoints

The exploratory PK objective for this study is to assess potential PK interactions between atezolizumab and Hu5F9-G4 on the basis of the following endpoints:

- Serum concentrations of atezolizumab given in combination with Hu5F9-G4 compared with atezolizumab given alone (based on historical data)
- Serum concentrations of Hu5F9-G4 given in combination with atezolizumab compared with Hu5F9-G4 given alone (based on historical data)

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- Complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete hematologic recovery (CRi), and CR with partial hematologic recovery (CRh) rate after up to 6 cycles of combination therapy, as determined by the investigator, according to the International Working Group (IWG) 2003 and European LeukemiaNet (ELN) 2010 criteria
- Duration of response (DOR), defined as the time from the initial response (CR, CRp, CRi, CRh, or partial remission [PR]) to the time of disease progression or death, whichever occurs first

Secondary Efficacy Objective

The secondary efficacy objective for this study is to make a preliminary assessment of the anti-neoplastic activity of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- Objective response rate achieved in the study, defined as the percentage of patients with a PR or better (i.e., CR + CRp + CRi + CRh + PR)
- Event-free survival, defined as the time from study entry to the date of induction treatment failure or relapse from CR, CRp, CRh, CRi, or death from any cause
- Leukemia-free survival, defined (only for patients achieving a CR, CRp, CRh, or CRi) as the time from the date of achievement of remission (CR, CRp, or CRi) until the date of relapse from CR, CRp, CRh, CRi, or death from any cause
- Overall survival, defined as time from study entry to the date of death from any cause
- Progression-free survival, defined as the time from the first day of study treatment to disease progression or death, whichever occurs first
- Rate of transfusion independence, defined as the percentage of patients who achieve transfusion independence (i.e., achieving any continuous 56-day window without requiring platelet or RBC transfusions) at any time during study treatment
- Duration of transfusion independence, defined as the number of consecutive days of transfusion independence, measured from 1 day after the last transfusion to disease progression or subsequent transfusion

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab and Hu5F9-G4 on the basis of the following endpoints:

- Incidence of anti-drug antibodies (ADAs) against atezolizumab during the study relative to the prevalence of ADAs at baseline
- Incidence of ADAs against Hu5F9-G4 during the study relative to the prevalence of ADAs at baseline

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to atezolizumab in combination with Hu5F9-G4 (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab and/or Hu5F9-G4, are associated with susceptibility to developing adverse events, can provide evidence of atezolizumab and/or Hu5F9-G4 activity, or can increase the knowledge and understanding of disease biology on the basis of the following endpoints:

- Relationship between biomarkers in blood and bone marrow (including somatic mutations) and efficacy, safety, PK, immunogenicity, expression profiles, bone marrow aspirate stromal factors, or other biomarker endpoints
- To determine the effect of single agent Hu5F9-G4 on T-cell activation and bone marrow infiltration in patients with R/R AML

Study Design

Description of Study

This is a Phase Ib, open-label, multicenter, non-randomized study of atezolizumab, evaluating the safety and pharmacokinetics of atezolizumab (an anti–PD-L1 monoclonal antibody) given in combination with Hu5F9-G4 (an anti-CD47 monoclonal antibody) for the treatment of patients with R/R AML (excluding promyelocytic leukemia).

An initial safety evaluation will be performed in 6 patients with relapsed AML. If atezolizumab in combination with Hu5F9-G4 is found to be initially safe and tolerable in patients with R/R AML, an additional cohort of 15 patients with R/R AML will be evaluated to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4.

If dose-limiting toxicities (DLTs) are observed in $\geq 33\%$ of patients (2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. If $< 33\%$ of the enrolled (1 patient or no patients) and dosed patients in any given cohort experience a DLT, an expansion cohort of 15 patients will be enrolled at the higher tolerated dose for this combination. If a dose de-escalation cohort is needed ($n = 12$ for safety cohorts), an expansion cohort of 9 patients will be enrolled at the lower tolerated dose for this combination.
The maximum number of patients enrolled in this study will be 21 patients (this number will include patients assessed for DLT plus those potentially removed prior to DLT assessment).

The proposed treatment regimen during Cycle 1 is a biomarker-driven treatment plan designed to assess the effect of single-agent Hu5F9-G4 on markers of immune activation in AML. This safety cohort is designed to assess the safety, tolerability, and clinical activity of Hu5F9-G4 in combination with atezolizumab based on the following schedule:

- Atezolizumab: Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles (Cycles 2 and beyond), 840 mg of IV atezolizumab will be given every 2 weeks (Q2W) on Days 8 and 22 of each 28-day cycle.
- Hu5F9-G4: Two priming doses of 1 mg/kg of Hu5F9-G4 will be administered to patients by continuous IV infusion on Days 1 and 4 of Cycle 1, followed by loading doses of 15 mg/kg IV on Day 8 and 30 mg/kg IV on Day 11. Starting on Day 15 of Cycle 1, Hu5F9-G4 maintenance will be given by IV infusion at a dose of 30 mg/kg once a week (QW) of each 28-day cycle. On days when both atezolizumab and Hu5F9-G4 are administered (Day 22 of Cycle 1 and Days 8 and 22 of subsequent cycles), Hu5F9-G4 should be administered first and *the interval between Hu5F9-G4 and atezolizumab infusions should follow guidelines as outlined in the protocol.*

If DLTs are observed in $\geq 33\%$ of patients (i.e., 2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. The dosing schedules for this de-escalation cohort will be as follows:

- Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles, 840 mg of atezolizumab administered by IV infusion will be given Q2W on Days 8 and 22 of each 28-day cycle.

- Hu5F9-G4 will be given as two priming doses of 1 mg/kg IV on Days 1 and 4, followed by loading doses of 10 mg/kg IV on Day 8 and 15 mg/kg on Day 11. Starting on Day 15, maintenance treatment with Hu5F9-G4 will be given by IV infusion at a dose of 15 mg/kg QW.
- If <33% *(i.e., 1 or* fewer of 6 patients) *patients in the de-escalation cohort experience a DLT,* an expansion cohort of 9 patients will be enrolled *to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4, using the same dosing regimen.*

If DLTs are observed in <33% of patients (*i.e., 1 or fewer of 6* patients) in the initial safety cohort, an expansion cohort of 15 patients will be enrolled to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4 using the same dosing regimen.

Study treatment will be administered until unacceptable toxicity or loss of clinical benefit, as determined by the investigator, after local biopsy results (if available) and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) are assessed.

Safety Evaluation Phase

Dose-Limiting Toxicity Assessment

The first 6 patients enrolled in the safety cohort will be eligible for DLT assessment. The DLT assessment window for the safety cohort is 56 days from the first dose of Hu5F9-G4.

All patients who experience a DLT during the DLT assessment window will be considered evaluable for safety evaluation decisions.

Patients who withdraw from study treatment (atezolizumab plus Hu5F9-G4) for any reason other than a DLT during this assessment window will not be considered evaluable for safety evaluation decisions and will be replaced. The total number of enrolled patients in this study will be capped at 21 patients. If patients are replaced prior to DLT assessment, discontinued patients will be counted toward the total limit of 21 patients.

During the DLT evaluation window, patients will not be allowed to make up missed doses; patients will resume dosing at their next scheduled dose. Patients who are unable to receive the next scheduled dose of Hu5F9-G4 or atezolizumab as a result of study treatment–related adverse events will be considered to have met the DLT criteria.

Rules for Dose Modification and Changes in Dose Scheduling following Dose-Limiting Toxicity

Dose modification following the DLT window will occur in accordance with the following rules:

- The safety cohort will enroll up to 6 patients.
- *If DLTs are observed in ≥33% of patients (i.e., 2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. The dosing schedules for this de-escalation cohort will be as follows:*
  - *Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles, 840 mg of atezolizumab administered by IV infusion will be given Q2W on Days 8 and 22 of each 28-day cycle.*
  - *Hu5F9-G4 will be given as two priming doses of 1 mg/kg IV on Days 1 and 4, followed by loading doses of 10 mg/kg IV on Day 8 and 15 mg/kg on Day 11. Starting on Day 15, maintenance treatment with Hu5F9-G4 will be given by IV infusion at a dose of 15 mg/kg QW.*
  - *If a DLT is observed in ≥33% of patients (i.e., 2 or more of 6 dose de-escalation patients), the dose and schedule will be considered intolerable and the MTD will have been exceeded.*
  - The dose level(s) and schedule at which *<33% of* patients (i.e., *1* or fewer of 6 *dose de-escalation* patients) experience a DLT will be declared the optimal dose and schedule *and an expansion cohort of 9 patients will be enrolled using the same dosing regimen.*

- *If DLTs are observed in <33% of patients (i.e., 1 or fewer of 6 patients) in the initial safety cohort, an expansion cohort of 15 patients will be enrolled to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4, using the same dosing regimen..*

Definition of Dose-Limiting Toxicity

A DLT is defined as any of the following adverse events that are causally related to study treatment that occur during the DLT assessment window and are considered by the investigator to be related to atezolizumab, *Hu5F9-G4*, or the combination of atezolizumab with Hu5F9-G4. For potential overlapping toxicities, investigators are encouraged to perform additional *testing, such as tissue biopsy, imaging, peripheral blood smears, immunological assays, and other laboratory studies* to determine the underlying etiology and appropriate attribution *(whether the event is related to atezolizumab, Hu5F9-G4, or the combination of atezolizumab and Hu5F9-G4. Testing is to be determined by the investigator, according to local medical standards, and if needed, in consultation with the Medical Monitor, based on an individual patient's clinical presentations. Testing may elucidate whether the event is an immune-mediated adverse event caused by atezolizumab, including those events that should be reported to the Sponsor immediately (i.e., within 24 hours)*.

Any of the following adverse events that occur during Cycles 1 *or 2* will be considered a DLT (if causality is determined to be yes according to Table 5) for atezolizumab alone or in combination with Hu5F9-G4:

- *Any adverse event (regardless of NCI CTCAE v5.0 grade) that leads to dose reduction or withdrawal*
- Any infusion-related toxicity Grade ≥ 3 (e.g., allergic reaction/hypersensitivity, fever, pain, bronchospasm, wheezing, or hypoxia)
- Hypocellular (≤ 5% cellularity) or aplastic bone marrow *≥3* without evidence of myeolodysplastic syndrome, leukemia, or infectious etiology that lasts for ≥ 35 days from the first occurrence
- *Grade ≥3 liver enzyme (ALT or AST) and Grade ≥3 creatinine elevations*
- Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding that requires transfusion of red cells and platelets
- *Grade ≥3 non-hematologic adverse events (with certain Grade 3 exceptions discussed below)*
- *Grade ≥4 neutropenia and thrombocytopenia lasting past Cycle 2 Day 28 in the absence of disease (defined as the presence of <5% bone marrow blasts)*

The following Grade 3 events will not be considered DLTs:

- Grade 3 nausea, vomiting, or diarrhea that resolves to Grade 1 or better within 7 days of supportive therapy *and does not require total parenteral nutrition, tube feeding, or prolonged hospitalization*
- Grade 3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care or resolves to become asymptomatic and/or Grade ≤ 2 within 7 days of supportive therapy
- Grade 3 fatigue*, asthenia, or fever* that resolves to Grade ≤ 2 within 7 days
- Grade 3 arthralgia that can be adequately managed with supportive therapy or that resolves to Grade ≤ 2 within 7 days
- *Asymptomatic* Grade 3 laboratory abnormalities *(other than liver enzyme and creatinine elevations)* that *resolve to Grade <2 within 72 hours*

All DLTs will be reported on an electronic Case Report Form (eCRF), the standard Adverse Event eCRF in the Sponsor's electronic data capture system within 24 hours. All DLTs will be considered adverse events of special interest for this protocol and will be reported to the Sponsor in an expedited manner. Dose modification decisions will be made by the Sponsor in consultation with investigators after review of available relevant data.

Stopping Rule for Excess Toxicity for Expansion Phase

Early stopping boundaries for the expansion cohort are based on the Pearson-Klopper confidence intervals of the observed toxicity rate, and a target toxicity rate of no more than 20%. The stopping boundary for a given number of enrolled patients is the minimum number of patients with excess toxicity that would lead to a toxicity rate with its lower 95% confidence boundary higher than 20%. During the expansion phase, an episode of excess toxicity will be defined as any adverse event meeting criteria for a DLT as outlined in the protocol.

Number of Patients

A total of 21 patients will be enrolled in this study at approximately 6–10 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Life expectancy of at least 12 weeks
- Eastern Cooperative Oncology Group Performance Status 0–2
- Ability to comply with the study protocol, in the investigator's judgment
- Documented and confirmed R/R AML *per WHO* classification, except acute promyelocytic leukemia*, and lack of response to all therapies of known benefit*

  Refractory AML is defined as failure to attain a CR following exposure to at least two courses of intensive induction regimens, six cycles of single-agent hypomethylating agent (HMA), or at least two cycles of venetoclax-containing regimens (combined to low-dose cytarabine or HMAs).

  Relapsed AML is defined as the morphological detection of ≥5% bone marrow blasts, reappearance of leukemic blasts in the blood, or development of extramedullary disease. For patients previously found to be in CR and minimal residual disease (MRD) negative (by flow cytometry), reappearance of a leukemic population by MRD testing can be classified as being relapsed AML (conversion from CR MRD negative to CR MRD positive).
- Adequate end-organ function, defined using the following laboratory parameters obtained within 28 days prior to the first dose of study drug:
  - AST, ALT, and ALP ≤ 2.5 × upper limit of normal (ULN)
  - Serum bilirubin ≤ 2 × ULN, with the following exception:

    Patients with known Gilbert disease or clear evidence of transfusion-related hemolysis who have serum bilirubin ≤ 3 × ULN may be enrolled. Cases of transfusion-related hemolysis must be discussed and approved by the Medical Monitor.
  - Serum creatinine ≤ 2 × ULN
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA < 500 IU/mL at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

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

- WBC count $\leq 20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each Hu5F9-G4 dose for Cycle 1

  Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea throughout the trial to reduce the WBC to $\leq 20 \times 10^3/\mu L$.
- Willingness and ability to provide pretreatment bone marrow aspirate and biopsy and agreement to provide subsequent bone marrow aspirates and biopsies during study treatment
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab and/or Hu5F9-G4, whichever is longer. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (tubal ligation, removal of ovaries and/or uterus).

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$per year during the treatment period and for at least 120 days after the final dose of atezolizumab and/or Hu5F9-G4. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 60 days after the final dose of atezolizumab and/or Hu5F9-G4 to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile: requirement for a negative serum pregnancy test result within 14 days prior to initiation of study treatment

<u>Exclusion Criteria</u>

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

- Previous allogeneic hematopoietic stem cell transplant within 6 months prior to enrollment, active graft versus host disease, or requiring transplant-related immunosuppression
- Prior solid organ transplant
- Evidence of active central nervous system (CNS) involvement by leukemia

  Patients with a history of leukemic CNS involvement that has been treated may have to undergo lumbar puncture and/or magnetic resonance imaging assessment prior to study entry at the discretion of the Medical Monitor.

- Pregnancy or lactation or intention to become pregnant during the study or within 5 months after the final dose of atezolizumab and/or Hu5F9-G4, whichever is longer

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- History of idiopathic pulmonary fibrosis, organizing pneumonitis (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis
- History of autoimmune disease
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement may be eligible for this study.
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen may be eligible for this study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of the following conditions are met:
  - Rash must cover $<10\%$ of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  - No occurrence of acute exacerbations of the underlying condition that require psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- Treatment with investigational therapy within 14 days prior to initiation of study drug
- Any approved AML-related therapy within 14 days prior to enrollment

  Granulocyte colony-stimulating factor to treat neutropenic fever and/or infection is permitted.

  Hydroxyurea may be used throughout the trial to control peripheral blood blast counts in response to the first dose of study treatment.
- Immunosuppressive therapy (including, but not limited to, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and anti–necrosis factor agents) within 6 weeks of Day 1 of Cycle 1
- Daily requirement for corticosteroids (>10 mg/day prednisone or equivalent, except for inhalation corticosteroids) within 2 weeks prior to Day 1 of Cycle 1
- Prior treatment with immune checkpoint blockade therapies (anti–CTLA-4, anti–PD-1, or anti–PD-L1) or immune agonists (anti-CD137, anti-CD40, and anti-OX40) or immune antagonists (anti-CD47)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon-α and interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to Day 1 of Cycle 1
- Treatment with denosumab (or other RANKL inhibitor) 4 weeks before the first dose and for 10 weeks after the final dose of atezolizumab

  Patients receiving denosumab therapy must be willing to be treated with a bisphosphonate while receiving study treatment.
- Administration of a live, attenuated vaccine within 4 weeks of Day 1 of Cycle 1 or anticipation that such a live, attenuated vaccine will be required during the study or within 5 months after the final dose of atezolizumab

  Influenza vaccination should be given during influenza season only (approximately October through May in the northern hemisphere and approximately April through September in the southern hemisphere). Patients must agree not to receive live, attenuated vaccines (e.g., FluMist®) within 28 days prior to enrollment, during treatment, or within 5 months following the final dose of atezolizumab.
- Planned major surgery during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment

- Poor peripheral venous access, unless prior central venous catheter placement has been performed
- Active infection

  Patients being treated for non-serious infectious complications (e.g., oral candidiasis or uncomplicated urinary tract infection) with oral or topical antimicrobials may be eligible for study treatment (antimicrobial treatment must be completed prior to Day 1 of Cycle 1 and cases must be discussed and approved by the Medical Monitor).
- Severe infection requiring hospitalization or IV antibiotics within 14 days prior to enrollment

  Patients receiving prophylactic antibiotics, antifungals, and antivirals as a result of prolonged neutropenia in the absence of active documented infection are eligible.

  Patients receiving IV antibiotics and hospitalization for febrile neutropenia may be eligible, where initial diagnosis of neutropenic fever was not due to any infectious etiology and the patient has been afebrile for $\geq$72 hours.
- Any serious medical condition or abnormality in clinical laboratory test results that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History or presence of an abnormal ECG finding that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, and evidence of prior myocardial infarction
- History of other malignancy within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year overall survival of $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells or any component of the atezolizumab, azacytidine, or Hu5F9-G4 formulation
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known allergy or hypersensitivity to any component of the atezolizumab and/or Hu5F9-G4 formulation

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs.

Length of Study

The last patient is expected to be enrolled *22* months after the first patient is enrolled, and the LPLV is expected to occur approximately *15* months after the last patient is enrolled. The total study duration is therefore expected to take approximately *37* months.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are atezolizumab and Hu5F9-G4.

Test Products (Investigational Drugs)

Atezolizumab

The dose level of atezolizumab in this study is 840 mg administered to patients by IV infusion on Days 8 and 22 of each 28-day cycle (Q2W) for patients enrolled in the safety cohort and in the expansion cohort. During the first cycle of treatment (Cycle 1), patients will receive 840 mg IV atezolizumab only on Day 22 in order to collect bone marrow and blood samples for biomarker assessment after steady state has been reached for Hu5F9-G4.

Hu5F9-G4

The initial priming dose will be administered as a continuous IV infusion in 250 mL of normal saline over 180 minutes to reduce the risk of acute hemagglutination. All other infusions for doses $>$1 mg/kg will be administered in 500 mL over 120 minutes. If more than 4 weeks have elapsed since the last dose of Hu5F9-G4 and the patient is to resume treatment, patients must undergo intra-patient dose escalation again of Hu5F9-G4 based on their original dosing regimen (e.g., 1 mg/kg of priming dose on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Days 11, 15, and 22).

The dose level of Hu5F9-G4 administered to patients by IV infusion in this study varies according to the week of treatment. Initially, two priming doses of 1 mg/kg will be given on Days 1 and 4 of Cycle 1. This will be followed by loading doses of 15 mg/kg on Day 8, followed by 30 mg/kg on Day 11 of Cycle 1. Starting on Day 15, Hu5F9-G4 maintenance will be given at a dose of 30 mg/kg QW.

Non-Investigational Medicinal Products

Premedication is required before administration of the first four doses of Hu5F9-G4 with 650–1000 mg of oral acetaminophen and 25–50 mg of oral or IV diphenhydramine or comparable regimen.

Statistical Methods

Primary Analysis

The safety analyses will include all patients who receive any amount of either study drug, with patients grouped as a whole.

Safety will be assessed through summaries of adverse events, change from baseline in targeted vital signs, laboratory test results, and physical examination findings.

All collected adverse event data will be listed by assigned dose level and patient number. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. DLTs and adverse events leading to treatment discontinuation will also be listed separately.

Determination of Sample Size

Design considerations covering all cohorts were not made with regard to explicit power and type I error considerations but to obtain preliminary safety, efficacy, PK, and pharmacodynamic information on atezolizumab in combination with Hu5F9-G4. The planned enrollment for this study is 21 patients, depending on the safety profile observed during the safety evaluation phase. The study will enroll approximately 6 patients in the safety cohort and approximately 15 patients in the expansion cohort. The sample size may increase as a result of dose findings. The probabilities of observing adverse events in at least 1 patient, given the varying actual adverse event rates, are listed in the following table.

Probability of Safety-Signal Detection with a Cohort of 21 Patients

True Underlying Probability of an Adverse Event	Probability of Observing at Least One Adverse Event in 21 Patients (%)
0.01	19.0
0.025	41.2
0.05	65.9
0.075	80.5
0.1	89.0

Interim Analysis

Interim looks may be performed during the study. Response data will be compared with the comparable historical data using statistical methodology such as a predictive and/or posterior probability design, with the modification that the uncertainty in the historical control data is fully taken into account by utilizing a distribution on the control response rate to enable internal decision-making for future development. The possible data sources to be used as historical controls may be publications, real-world data sources, and other reliable information on efficacy from other studies in similar patient groups that will be available by the time of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
allo-HSCT	allogeneic hematopoietic stem cell transplant
AML	acute myeloid leukemia
anti–CTLA-4	anti–cytotoxic T lymphocyte–associated protein 4
CDC	complement-dependent cytotoxicity
C_{max}	maximum concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
Fc	fragment crystallizable
FDA	(U.S.) Food and Drug Administration
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HMA	hypomethylating agent
IAP	integrin-associated protein
ICH	International Council for Harmonisation
IDH1 (2)	isocitrate dehydrogenase 1 (2)

Abbreviation	Definition
IFN-α	interferon-α
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
IWG	International Working Group
IxRS	interactive voice or web-based response system
LDAC	low-dose cytarabine
LFS	leukemia-free survival
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PO	by mouth; orally
PR	partial remission
Q2W	every 2 weeks
Q3W	every 3 weeks
QTcF	QT interval corrected through use of Fridericia's formula
QW	once a week
RBR	Research Biosample Repository
Rh	Rhesus (factor)
R/R	relapsed and/or refractory (acute myeloid leukemia)
QTcF	QT interval corrected through use of Fridericia's formula

Abbreviation	Definition
SIRPα	signal regulatory protein–α
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a hematopoietic neoplasm that is characterized by rapid proliferation, clonal heterogeneity, and abnormal differentiation. Until recently, the general management strategy for patients with AML had not changed significantly over the last three decades.

The initial assessment of patients with AML is to determine whether a patient is a candidate for intensive induction chemotherapy. If a complete remission (CR) is achieved with a cytarabine and an anthracycline-containing regimen (i.e., 7+3+ fractionated gemtuzumab ozogamicin, 7+3+ midostaurin for *FLT3*-mutated AML, or liposomal daunorubicin plus cytarabine for higher-risk AML), then post-remission chemotherapy (i.e., consolidation) is administered. Depending on cytogenetic and/or molecular prognostic markers, allogeneic hematopoietic stem cell transplantation (allo-HSCT) may be recommended after achieving the first CR, provided a donor source is available and the patient remains in good health.

Treatment with high-dose chemotherapy regimens can cure 35%–40% of adults who are < 60 years old (Döhner et al. 2010). However, the cure rate is much lower (5%–15%) in patients who are 60 years or older. Outcomes are even worse in older patients who are unable to receive induction chemotherapy or allo-HSCT, with a median survival of just 5–10 months. Such patients are often treated palliatively with hypomethylating agents (HMAs) (azacitidine, decitabine) or low-dose cytarabine (LDAC).

A Phase III study of decitabine versus a conventional-care regimen (LDAC was the most common choice) determined that treatment with decitabine was associated with a survival advantage (7.7 vs. 5 months) but did not meet the predefined threshold for statistical significance (Kantarjian et al. 2012). Nevertheless, the European Medicines Agency (EMA), but not the U.S. Food and Drug Administration (FDA), has approved the use of both decitabine and azacitidine in older patients with AML. The Phase III AML-001 study of azacitidine versus a conventional-care regimen also showed increased survival with azacitidine (10.4 vs. 6.5 months); this difference was not statistically significant but can be viewed as clinically meaningful (Dombret et al. 2015). More recently, the combination of venetoclax plus HMA therapy has shown to be a novel, well-tolerated regimen with clinically promising activity in patients with AML. Approval by the U.S. FDA is anticipated by the fourth quarter of 2018.

Response to treatment during relapse from remission depends on the length of remission and other prognostic factors, with longer duration of remission and lack of poor prognostic factors (e.g., prior allo-HSCT, complex cytogenetics, and older age) associated with better responses to salvage chemotherapy and prolonged survival (Breems et al. 2005). There is no consensus standard of care in this setting. In fit patients, the goal is to treat with an intensive salvage chemotherapy regimen, followed by an allo-HSCT if a CR is achieved.

One of the most challenging situations in AML management remains for patients who do not respond to initial chemotherapy (10%–40% of patients) (Thol et al. 2015). Here, the data are very limited, but the approach is the same as in the relapsed setting: high-intensity salvage chemotherapy followed by allo-HSCT. Over the past 12 months, three new small molecule inhibitors have shown promising clinical activity in patients with relapsed and/or refractory (R/R) AML. Inhibitors of the isocitrate dehydrogenase 1 and 2 enzymes (IDH1 and IDH2 inhibitors) have shown promising single-agent activity in IDH1-and IDH2-mutated AML, respectively. Enasidenib (an IDH2 inhibitor) was recently approved by the U.S. FDA for the treatment of R/R IDH2-mutated AML, as was ivosidenib (an IDH1 inhibitor). For patients with *FLT3*-mutated AML, the QuANTUM-R trial recently demonstrated improved responses and overall survival (OS) in patients randomized to receive quizartinib; the drug has received fast-track designation for filing to the FDA. Despite recent improvements, all phases of AML treatment remain areas of high unmet medical need; however, the need is most pressing in the R/R and older, treatment-naive, chemotherapy unfit populations.

1.2 BACKGROUND ON ATEZOLIZUMAB

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

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

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

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

1.2.1 Atezolizumab Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to assess the in vitro and in vivo activity to determine in vivo pharmacokinetic (PK) behavior, to evaluate the safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with atezolizumab. The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab to cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks for patients.

Refer to the latest version of the Atezolizumab Investigator's Brochure for details with regard to the nonclinical studies.

1.2.2 Atezolizumab Clinical Pharmacokinetics and Immunogenicity

Exposure to atezolizumab increased proportionally over the dose range of 1–20 mg/kg, which included the fixed dose of 1200 mg administered every 3 weeks (Q3W). On the basis of a population-PK analysis that included 472 patients in the dose range of 1–20 mg/kg, the typical population clearance was 0.20 L/day, the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. The population-PK analysis suggested that steady state was obtained after 6–9 weeks (two to three cycles) of repeated dosing. The systemic accumulation in area under the concentration–time curve, maximum concentration, and trough concentration was 1.91-, 1.46-, and 2.75-fold, respectively. Subsequent PK studies support the use of 840 mg of atezolizumab every 2 weeks and 1640 mg of atezolizumab every 4 weeks.

The development of anti-therapeutic antibodies (ADAs) to atezolizumab has been observed in patients in all dose cohorts and has been associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ADAs has not had a significant impact on atezolizumab pharmacokinetics for doses from 10 to 20 mg/kg. Patients receiving the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough concentrations of drug

despite the detection of ADAs. To date, no clear relationship between detection of ADAs and adverse events or infusion reactions has been observed.

See the Atezolizumab Investigator's Brochure for additional details on clinical pharmacokinetics and immunogenicity.

1.2.3 Atezolizumab Clinical Studies

For details of additional ongoing studies, refer to the latest version of the Atezolizumab Investigator's Brochure.

1.2.4 Atezolizumab Clinical Safety

As of 17 May 2018, an estimated 16,000 or more patients with solid tumor and hematologic malignancies had received atezolizumab in clinical trials as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy. Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

For updated single-agent efficacy and adverse event profile, please refer to Atezolizumab Investigator's Brochure. The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment.

The percentage of patients who discontinued atezolizumab because of any adverse event is consistent when given as a single agent or in combination with chemotherapy (e.g., 5.4% in Study PCD4989g and 5.8% in Study GP28328, respectively). The percentage of patients with any Grade 5 adverse event was similar when atezolizumab was given as a single agent or in combination with chemotherapy (e.g., 1.6% in Study PCD4989g and 1.0% in Study GP28328).

Immune-mediated adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events are closely monitored during the atezolizumab clinical program. To date, immune-mediated adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome and/or myasthenia gravis, meningoencephalitis, and myocarditis, hypophysitis, nephritis, and myositis.

Overall, most of the immune-mediated adverse events observed with atezolizumab have been mild and self-limiting. Immune-mediated adverse events should be recognized

early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

More recently, atezolizumab has been tested in patients with advanced myeloid malignancies (i.e., myelodysplastic syndrome [MDS] and AML) as a single agent and in combination with HMAs (both in the front-line and the R/R settings). In MDS, the single-agent adverse event profile did not demonstrate any unexpected toxicities. However, an increased rate of fatal adverse events was observed in patients receiving atezolizumab in combination with azacitidine given as front-line therapy compared with published rates for all deaths with azacytidine monotherapy in the first 3 months (28.6% vs. 11%, respectively) (Gerds et al. 2017). In addition, the overall safety profile (Grade 3 and 4 serious adverse events and adverse events leading to discontinuation) of atezolizumab plus azacitidine is worse than azacitidine monotherapy. The overall rate of infections appears to be higher for the combination than what is reported in the literature for azacitidine monotherapy in the front-line treatment setting for MDS and best supportive care in R/R MDS, which was not expected based on the mechanism of action and single-agent data.

In AML, the single-agent adverse event profile did not demonstrate any unexpected toxicities, but no evidence of clinical benefit was noted. The combination study of guadecitabine plus atezolizumab was stopped early based on the increased early death rate observed in previously untreated patients with MDS treated with azacitidine plus atezolizumab.

Refer to the Atezolizumab Investigator's Brochure for details on adverse events observed in patients treated with atezolizumab monotherapy or in combination with other agents and for details on immune-mediated adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events can be found in the Atezolizumab Investigator's Brochure.

1.3 BACKGROUND ON Hu5F9-G4

Hu5F9-G4 is a recombinant humanized anti-CD47 monoclonal antibody of the IgG4 κ isotype containing a Ser-Pro substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. Hu5F9-G4 is a first-in-class anti-cancer therapeutic agent targeting the CD47/SIRPα axis.

Hu5F9-G4 is secreted by a genetically engineered CHOK1SV™ cell line as a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy γ chains and two identical 219 amino acid κ light chains. The molecular formula for Hu5F9-G4 is C6462H9960N1718O2027S48, and the predicted molecular weight is 145687.6 daltons based on the amino acid sequence and excluding contributions from N-linked glycosylation.

Binding of Hu5F9-G4 to human CD47 on target malignant cells blocks the “don’t eat me” signal to macrophages and enhances tumor cell phagocytosis. In addition, Hu5F9-G4 elicits an anti-tumor T-cell response by means of phagocyte-mediated cross-presentation of tumor antigens to T cells (Tseng et al. 2013). CD47 is a 50-kD cell surface glycoprotein that is widely expressed on cancer cells and in normal tissues (Brown and Franzier 2001). CD47 consists of an extracellular Ig superfamily domain linked to five transmembrane spanning regions and a short intracellular cytoplasmic domain (Brown and Franzier 2001). It binds to a variety of integrins and thrombospondin-1; however, its interaction with SIRPα is thought to be the major mediator of its function as a negative checkpoint regulator of phagocytosis.

CD47 binding to the receptor SIRPα on the surface of cells of the innate immune system, such as macrophages and dendritic cells, initiates a signal transduction cascade that blocks phagocytosis. In this way, CD47 functions as an inhibitor of phagocytosis by delivering a dominant inhibitory signal to phagocytic cells (Blazar et al. 2001; Okazawa et al. 2005). However, the complex process of phagocytosis depends on the relative balance of pro-phagocytic and anti-phagocytic inputs. Most normal cells, apart from aging RBCs (Oldenborg et al. 2000; Okazawa et al. 2005), lack expression of pro-phagocytic signals (Jaiswal et al. 2009; Majeti et al. 2009; Chao et al. 2012) and are unaffected by CD47 blockade. In contrast, most cancer cells express pro-phagocytic signals on their cell surface, many of which are not yet molecularly characterized (Chao et al. 2012). As a consequence, effective phagocytosis requires two events: silencing of the CD47/SIRPα inhibition pathway and interaction of the pro-phagocytic signal with its receptor. Cancer cells uniformly exhibit increased expression of CD47, presumably to prevent phagocytic elimination by innate immune cells (Jaiswal et al. 2010). When CD47 is blocked from interacting with SIRPα (e.g., using an antibody to CD47), pro-phagocytic signals dominate, enabling phagocytosis of the cancer cells, which results in inhibition of tumor growth and metastasis.

Hu5F9-G4 is an anti-human CD47 monoclonal antibody that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells (Liu et al. 2015). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, Hu5F9-G4 was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells (Liu et al. 2015). Preclinical studies using xenograft cancer models provide compelling evidence that Hu5F9-G4 triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on the mechanism of action and its potent preclinical activity, Hu5F9-G4 is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

Data from several studies indicate that the mechanism of action of Hu5F9-G4 does not involve Fc-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effector functions. In order to reduce the potential for cytotoxicity against normal CD47-expressing cells, Hu5F9-G4 was constructed on a human IgG4 isotype scaffold to minimize the recruitment of Fc-dependent effector functions such as ADCC and CDC. Several cell-based studies were subsequently performed to assess the ability of Hu5F9-G4 to stimulate ADCC or CDC activity, in which Fc-mediated ADCC or CDC effector functions were not observed.

1.3.1 Hu5F9-G4 Nonclinical Studies

Nonclinical safety assessment of Hu5F9-G4 was performed in non-human primates (i.e., cynomolgus and rhesus monkeys). Binding affinity studies demonstrated that Hu5F9-G4 binds to human CD47 and cynomolgus monkey CD47 with high affinity (dissociation constant = 8.0 pM and 10 pM, respectively). In contrast, Hu5F9-G4 (and its parent 5F9) does not bind to mouse CD47.

The therapeutic effect of Hu5F9-G4 on human AML was evaluated in human patient AML xenograft tumor models in vivo with two independent primary patient samples (SU028 and SU048). Six weeks after xenotransplantation, therapy was initiated with daily intraperitoneal injections of either control mouse IgG or 100 μg of Hu5F9-G4 (5 mice per treatment cohort for each patient AML xenograft model). Daily doses of 100 μg of Hu5F9-G4 over 2 weeks cleared AML in the bone marrow of all mice at the end of treatment with recovery of normal hematopoiesis in the bone marrow, leading to a major survival benefit compared with control cohorts. Serum levels of 50–150 μg/mL of Hu5F9-G4 were achieved after 2 weeks of treatment.

In studies designed to explore the dose-dependent therapeutic efficacy of Hu5F9-G4 on human AML in a human patient AML xenograft tumor model in vivo, daily doses of 100 μg of Hu5F9-G4 or twice weekly doses of 500 μg of Hu5F9-G4 eradicated AML after 2 weeks of treatment in the majority of mice. In addition, 3 of 16 mice (2 in the 100-μg Hu5F9-G4 treatment group and 1 in the 500-μg Hu5F9-G4 treatment group) were not cured after the first treatment course. Re-treatment resulted in a significant reduction of AML burden in the bone marrow and long-term remission. However, 2 mice relapsed again after 5 months and therefore received a third and fourth treatment course with Hu5F9-G4, but the mice either did not respond or relapsed again after a 2-month remission.

In xenografted mice with very high circulating leukocytes (> 50% of total WBC count) and marrow infiltration with AML (> 80%), Hu5F9-G4 treatment caused death within 1 hour of administration of the first dose. In all cases in which mice were xenografted with primary human solid tumors, the mice did not have a high level of circulating tumor burden.

For full details on Hu5F9-G4 nonclinical studies, please refer to the Hu59-G4 Investigator's Brochure.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008) (see Atezolizumab Investigator's Brochure for details).

Clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012). However, clinical trials of patients with myeloid malignancies have shown disappointing results.

Similarly, the ongoing Phase I clinical trial (SCI-CD47-002), testing single-agent Hu5F9-G4 (an anti-CD47 monoclonal antibody), has not demonstrated significant activity in patients with R/R AML. Reduction in bone marrow blast count and prolonged stable disease have been observed.

Single-agent atezolizumab has been generally well tolerated in patients with advanced myeloid malignancies (see Atezolizumab Investigator's Brochure for detailed safety results). In advanced myeloid malignancies, the percentage of patients discontinuing single-agent atezolizumab because of adverse events was low (10%). Similarly, no safety concerns have been identified in patients with AML who have been treated with single-agent Hu5F9-G4. To date, no DLTs were documented and no study treatment–related deaths have been observed. No MTD has been defined for this agent (for details, see the Hu5F9-G4 Investigator's Brochure for detailed safety results).

As of the clinical cutoff date (1 March 2017), no DLTs had occurred in the 13 patients treated in Study SCI-CD47-002. A DLT of Grade 3 anemia, which was assessed as related to Hu5F9-G4, was reported for the first patient treated. Because this patient had baseline Grade 3 anemia prior to treatment and given that Grade 3 anemia is common at baseline in patients with R/R AML, Grade 3 anemia was subsequently removed as a DLT. No additional DLTs have been reported since that first patient.

As of the clinical cutoff date, a total of 27 serious adverse events had been reported. Of these events, 25 events were assessed by the investigator to be unrelated to study treatment and two events were assessed as related to study treatment (two events of anemia and one event of blood and lymphatic system disorders reported for 1 patient and one event of pyrexia). All events have resolved.

Despite limited single-agent activity reported with both investigational agents when used as single agents, preclinical data have demonstrated that Hu5F9-G4 elicits an anti-tumor

T-cell response (see the Hu5F9-G4 Investigator's Brochure for full details). In addition, pharmacodynamic (PD) assessment of bone marrow biopsies from patients with AML demonstrated a significant increase in the bone marrow infiltrate of T cells with Hu5F9-G4 treatment. CD47 blockade leads to tumor cell phagocytosis by macrophages and subsequent cross-presentation of tumor antigens by macrophages and other antigen-presenting cells to CD8 T-cells, eliciting an adaptive immune cell response (Tseng et al. 2013). Anti–PD-1)/PD-L1 antibodies enable enhanced T-cell activity through blockade of T-cell checkpoint inhibition and reversal of T-cell exhaustion. Thus, the combination of Hu5F9-G4 with an anti–PD-1/PD-L1 antibody can lead to an enhanced T-cell anti-tumor response through these complementary mechanisms of action.

This study will enroll patients with R/R AML. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for clinical trials of novel therapeutic candidates. The benefit–risk ratio for atezolizumab in combination with Hu5F9-G4 is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

This Phase Ib study is designed to evaluate the safety and pharmacokinetics of atezolizumab when given in combination with Hu5F9-G4 to patients with R/R AML. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab and Hu5F9-G4).

2.1 SAFETY OBJECTIVE

The primary safety objective for this study is to characterize the safety and tolerability of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- Incidence of adverse events, with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Change from baseline in physical examination findings

2.2 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab and Hu5F9-G4 when administered in combination to patients with R/R AML on the basis of the following endpoints:

- Serum concentrations of atezolizumab
- Serum concentrations of Hu5F9-G4 at specified timepoints

The exploratory PK objective for this study is to assess potential PK interactions between atezolizumab and Hu5F9-G4 on the basis of the following endpoints:

- Serum concentrations of atezolizumab given in combination with Hu5F9-G4 compared with atezolizumab given alone (based on historical data)
- Serum concentrations of Hu5F9-G4 given in combination with atezolizumab compared with Hu5F9-G4 given alone (based on historical data)

2.3 EFFICACY OBJECTIVES

2.3.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- CR, CR with incomplete platelet recovery (CRp), CR with incomplete hematologic recovery (CRi), and CR with partial hematologic recovery (CRh) rate after up to 6 cycles of combination therapy, as determined by the investigator, according to the International Working Group (IWG) 2003 and European LeukemiaNet (ELN) 2010 criteria (Döhner et al. 2017)
- Duration of response (DOR), defined as the time from the initial response (CR, CRp, CRi, CRh, or partial remission [PR]) to the time of disease progression or death, whichever occurs first

2.3.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to make a preliminary assessment of the anti-neoplastic activity of atezolizumab administered in combination with Hu5F9-G4 to patients with R/R AML on the basis of the following endpoints:

- Objective response rate (ORR) achieved in the study, defined as the percentage of patients with a PR or better (i.e., CR + CRp + CRi + CRh + PR)
- Event-free survival (EFS), defined as the time from study entry to the date of induction treatment failure or relapse from CR, CRp, CRh, CRi, or death from any cause
- Leukemia-free survival (LFS), defined (only for patients achieving a CR, CRp, CRh, or CRi) as the time from the date of achievement of remission (CR, CRp, or CRi) until the date of relapse from CR, CRp, CRh, CRi, or death from any cause
- OS, defined as time from study entry to the date of death from any cause
- Progression-free survival (PFS), defined as the time from the first day of study treatment to disease progression or death, whichever occurs first
- Rate of transfusion independence, defined as the percentage of patients who achieve transfusion independence (i.e., achieving any continuous 56-day window without requiring platelet or RBC transfusions) at any time during study treatment

- Duration of transfusion independence, defined as the number of consecutive days of transfusion independence, measured from 1 day after the last transfusion to disease progression or subsequent transfusion

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab and Hu5F9-G4 on the basis of the following endpoints:

- Incidence of ADAs against atezolizumab during the study relative to the prevalence of ADAs at baseline
- Incidence of ADAs against Hu5F9-G4 during the study relative to the prevalence of ADAs at baseline

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to atezolizumab in combination with Hu5F9-G4 (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab and/or Hu5F9-G4, are associated with susceptibility to developing adverse events, can provide evidence of atezolizumab and/or Hu5F9-G4 activity, or can increase the knowledge and understanding of disease biology on the basis of the following endpoints:

- Relationship between biomarkers in blood and bone marrow (including somatic mutations) (listed in Section 4.5.7.2) and efficacy, safety, PK, immunogenicity, expression profiles, bone marrow aspirate stromal factors, or other biomarker endpoints
- To determine the effect of single agent Hu5F9-G4 on T-cell activation and bone marrow infiltration in patients with R/R AML

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib, open-label, multicenter, non-randomized study of atezolizumab, evaluating the safety and pharmacokinetics of atezolizumab (an anti–PD-L1 monoclonal antibody) given in combination with Hu5F9-G4 (an anti-CD47 monoclonal antibody) for the treatment of patients with R/R AML (excluding promyelocytic leukemia).

An initial safety evaluation will be performed in 6 patients with relapsed AML. If atezolizumab in combination with Hu5F9-G4 is found to be initially safe and tolerable in patients with R/R AML, an additional cohort of 15 patients with R/R AML will be evaluated to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4.

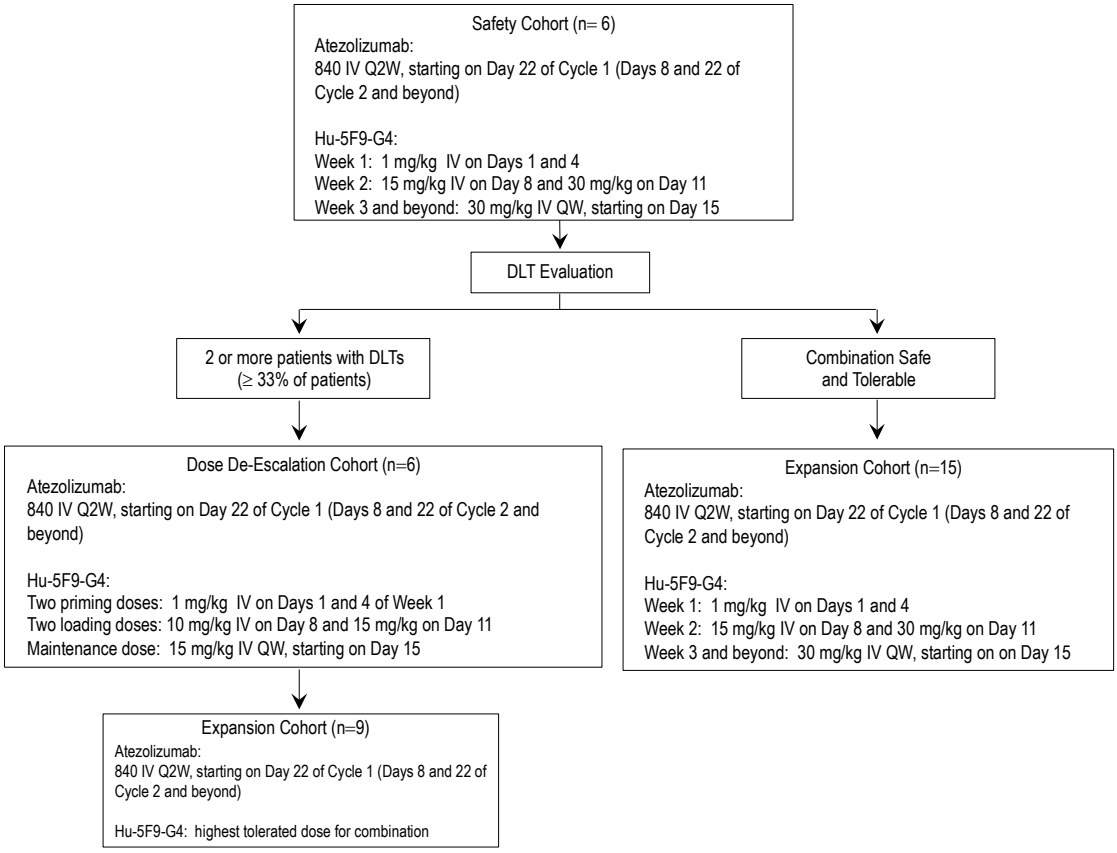
If DLTs are observed in $\geq$33% of patients (i.e., 2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. If $<$33% of the enrolled (1 patient or no patients) and dosed patients in any given cohort experience a

DLT, an expansion cohort of 15 patients will be enrolled at the higher tolerated dose for this combination. If a dose de-escalation cohort is needed (n = 12 for safety cohorts), an expansion cohort of 9 patients will be enrolled at the lower tolerated dose for this combination. The maximum number of patients enrolled in this study will be 21 patients (this number will include patients assessed for DLT plus those potentially removed prior to DLT assessment).

3.1.1 Overview of Study Design

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

Figure 1 Study Schema



Atezo = atezolizumab; DLT = dose-limiting toxicity; Q2W = every 2 weeks; QW = once a week.

Note: On days when both atezolizumab and Hu5F9-G4 are administered (Day 22 of Cycle 1 and Days 8 and 22 of subsequent cycles), Hu5F9-G4 should be administered first and *the interval between Hu5F9-G4 and atezolizumab infusions should follow guidelines as outlined in Table 2.*

The proposed treatment regimen during Cycle 1 is a biomarker-driven treatment plan designed to assess the effect of single-agent Hu5F9-G4 on markers of immune activation in AML. This safety cohort is designed to assess the safety, tolerability, and clinical activity of Hu5F9-G4 in combination with atezolizumab based on the following schedule:

- Atezolizumab: Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles (Cycles 2 and beyond), 840 mg of IV atezolizumab will be given every 2 weeks (Q2W) on Days 8 and 22 of each 28-day cycle.
- Hu5F9-G4: Two priming doses of 1 mg/kg of Hu5F9-G4 will be administered to patients by continuous IV infusion on Days 1 and 4 of Cycle 1, followed by loading doses of 15 mg/kg IV on Day 8 and 30 mg/kg IV on Day 11. Starting on Day 15 of Cycle 1, Hu5F9-G4 maintenance will be given by IV infusion at a dose of 30 mg/kg once a week (QW) of each 28-day cycle. On days when both atezolizumab and Hu5F9-G4 are administered (Day 22 of Cycle 1 and Days 8 and 22 of subsequent cycles), Hu5F9-G4 should be administered first and *the interval between Hu5F9-G4 and atezolizumab infusions should follow guidelines as outlined in Table 2*.

If DLTs are observed in ≥33% of patients (i.e., 2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. The dosing schedules for this de-escalation cohort will be as follows:

- Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles, 840 mg of atezolizumab administered by IV infusion will be given Q2W on Days 8 and 22 of each 28-day cycle.
- Hu5F9-G4 will be given as two priming doses of 1 mg/kg IV on Days 1 and 4, followed by loading doses of 10 mg/kg IV on Day 8 and 15 mg/kg on Day 11. Starting on Day 15, maintenance treatment with Hu5F9-G4 will be given by IV infusion at a dose of 15 mg/kg QW.
- If <33% *(i.e., 1 or* fewer of 6 patients) *patients in the de-escalation cohort experience a DLT,* an expansion cohort of 9 patients will be enrolled *to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4, using the same dosing regimen*

If DLTs are observed in <33% of patients (*i.e., 1 or fewer of 6* patients) in the initial safety cohort, an expansion cohort of 15 patients will be enrolled to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4, using the same dosing regimen.

Study treatment will be administered until unacceptable toxicity or loss of clinical benefit, as determined by the investigator, after local biopsy results (if available) and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) are assessed.

3.1.2 Safety Evaluation Phase

3.1.2.1 Dose-Limiting Toxicity Assessment

The first 6 patients enrolled in the safety cohort will be eligible for DLT assessment. The DLT assessment window for the safety cohort is 56 days from the first dose of Hu5F9-G4.

All patients who experience a DLT during the DLT assessment window will be considered evaluable for safety evaluation decisions.

Patients who withdraw from study treatment (atezolizumab plus Hu5F9-G4) for any reason other than a DLT during this assessment window will not be considered evaluable for safety evaluation decisions and will be replaced. The total number of enrolled patients in this study will be capped at 21 patients. If patients are replaced prior to DLT assessment, discontinued patients will be counted toward the total limit of 21 patients.

During the DLT evaluation window, patients will not be allowed to make up missed doses; patients will resume dosing at their next scheduled dose. Patients who are unable to receive the next scheduled dose of Hu5F9-G4 or atezolizumab as a result of study treatment–related adverse events will be considered to have met the DLT criteria.

3.1.2.2 Rules for Dose Modification and Changes in Dose Scheduling following Dose-Limiting Toxicity

Dose modification following the DLT window will occur in accordance with the following rules:

- The safety cohort will enroll up to 6 patients.
- *If DLTs are observed in ≥33% of patients (i.e., 2 or more of 6 patients) in this initial safety cohort, a dose de-escalation cohort of 6 patients will be enrolled. The dosing schedules for this de-escalation cohort will be as follows:*
  - *Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles, 840 mg of atezolizumab administered by IV infusion will be given Q2W on Days 8 and 22 of each 28-day cycle.*
  - *Hu5F9-G4 will be given as two priming doses of 1 mg/kg IV on Days 1 and 4, followed by loading doses of 10 mg/kg IV on Day 8 and 15 mg/kg on Day 11. Starting on Day 15, maintenance treatment with Hu5F9-G4 will be given by IV infusion at a dose of 15 mg/kg QW.*
  - *If a DLT is observed in ≥33% of patients (i.e., 2 or more of 6 dose de-escalation patients), the dose and schedule will be considered intolerable and the MTD will have been exceeded.*

  - The dose level(s) and schedule at which *<33% of* patients (i.e., *1* or fewer of 6 *dose de-escalation* patients) experience a DLT will be declared the optimal dose and schedule *and an expansion cohort of 9 patients will be enrolled using the same dosing regimen.*

- *If DLTs are observed in <33% of patients (i.e., 1 or fewer of 6 patients) in the initial safety cohort, an expansion cohort of 15 patients will be enrolled to further test the safety and anti-tumor activity of atezolizumab in combination with Hu5F9-G4, using the same dosing regimen.*

3.1.2.3 Definition of Dose-Limiting Toxicity

A DLT is defined as any of the following adverse events that are causally related to study treatment that occur during the DLT assessment window and are considered by the investigator to be related to atezolizumab*, Hu5F9-G4*, or the combination of atezolizumab with Hu5F9-G4 (see Section 5.3.4, Table 5, for guidance on causal attribution). For potential overlapping toxicities, investigators are encouraged to perform additional *testing, such as tissue biopsy, imaging, peripheral blood smears, immunological assays, and other laboratory studies* to determine the underlying etiology and appropriate attribution *(whether the event is related to atezolizumab, Hu5F9-G4, or the combination of atezolizumab and Hu5F9-G4. Testing is to be determined by the investigator, according to local medical standards, and if needed, in consultation with the Medical Monitor, based on an individual patient's clinical presentations. Testing may elucidate whether the event is an immune-mediated adverse event caused by atezolizumab, including those events listed in Section 5.2.3 that should be reported to the Sponsor immediately (i.e., within 24 hours).*

Any of the following adverse events that occur during Cycles 1 *or 2* will be considered a DLT (if causality is determined to be yes according to Table 5) for atezolizumab alone or in combination with Hu5F9-G4:

- *Any adverse event (regardless of NCI CTCAE v5.0 grade) that leads to dose reduction or withdrawal*
- Any infusion-related toxicity Grade ≥3 (e.g., allergic reaction/hypersensitivity, fever, pain, bronchospasm, wheezing, or hypoxia)
- Hypocellular (≤5% cellularity) or aplastic bone marrow *≥3* without evidence of MDS, leukemia, or infectious etiology that lasts for ≥35 days from the first occurrence
- *Grade ≥3 liver enzyme (ALT or AST) and Grade ≥3 creatinine elevations*
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding that requires transfusion of red cells and platelets
- *Grade ≥3 non-hematologic adverse events (with certain Grade 3 exceptions discussed below)*
- *Grade ≥4 neutropenia and thrombocytopenia lasting past Cycle 2 Day 28 in the absence of disease (defined as the presence of <5% bone marrow blasts)*

The following Grade 3 events will not be considered DLTs:

- Grade 3 nausea, vomiting, or diarrhea that resolves to Grade 1 or better within 7 days of supportive therapy *and does not require total parenteral nutrition, tube feeding, or prolonged hospitalization*
- Grade 3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care (for further details see the Atezolizumab Investigator's Brochure) or resolves to become asymptomatic and/or Grade ≤2 within 7 days of supportive therapy
- Grade 3 fatigue*, asthenia, or fever* that resolves to Grade ≤2 within 7 days
- Grade 3 arthralgia that can be adequately managed with supportive therapy or that resolves to Grade ≤2 within 7 days
- *Asymptomatic* Grade 3 laboratory abnormalities *(other than liver enzyme and creatinine elevations)* that *resolve to Grade <2 within 72 hours*

All DLTs will be reported on an electronic Case Report Form (eCRF), the standard Adverse Event eCRF in the Sponsor's electronic data capture (EDC) system within 24 hours (see Section 5.3.5). All DLTs will be considered adverse events of special interest for this protocol and will be reported to the Sponsor in an expedited manner, as indicated in Section 5.2.3. Dose modification decisions will be made by the Sponsor in consultation with investigators after review of available relevant data.

3.1.2.4 *Stopping Rule for Excess Toxicity for Expansion Phase*

Early stopping boundaries for the expansion cohort are based on the Pearson-Klopper confidence intervals of the observed toxicity rate, and a target toxicity rate of no more than 20%. The stopping boundary for a given number of enrolled patients is the minimum number of patients with excess toxicity that would lead to a toxicity rate with its lower 95% confidence boundary higher than 20% (see Table 1. During the expansion phase, an episode of excess toxicity will be defined as any adverse event meeting criteria for a DLT as outlined in Section 3.1.2.3.

Table 1 Early Stopping Boundaries for Expansion Cohort

Number of Patients Enrolled	*Stopping Boundary (Number of Patients Who Experience Excess Toxicity)*	*Observed Toxicity Rate* [a]	*95% Confidence Interval*
3	*3*	*100%*	*(29%, 100%)*
4	*4*	*100%*	*(40%, 100%)*
5	*4*	*80%*	*(28%, 99%)*
6	*4*	*78%*	*(22%, 96%)*
7	*5*	*71%*	*(29%, 96%))*
8	*5*	*62.5%*	*(24%, 91%)*
9	*5*	*56%*	*(21%, 86%)*
10	*6*	*60%*	*(26%, 88%)*
11	*6*	*55%*	*(23%, 83%)*
12	*6*	*50%*	*(21%, 79%)*
13	*7*	*54%*	*(25%, 81%)*
14	*7*	*50%*	*(23%, 77%)*
15	*7*	*47%*	*(21%, 73%)*

[a] *The confidence interval for the observed toxicity rate calculated based on the Pearson-Klopper method.*

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The last patient is expected to be enrolled *22* months after the first patient is enrolled, and the LPLV is expected to occur approximately *15* months after the last patient is enrolled. The total study duration is therefore expected to take approximately *37* months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 840 mg IV Q2W (840 mg on Days 8 and 22 of each 28-day cycle). The exception will occur at Cycle 1, when only 1 cycle dose of atezolizumab will be administered at a fixed dose of 840 mg IV on Day 22 (biomarker-driven treatment schedule). *The starting dose and schedule of atezolizumab 840 mg IV Q2W is currently approved in the United States in several indications, including urothelial carcinoma, non–small cell lung cancer, triple-negative breast cancer, and small cell lung cancer (Tecentriq® U.S. Package Insert). Based on the mechanism of action of the drug, pathophysiology of disease, and study population characteristics, it is not expected that the safety profile would be different for the AML population. Thus, atezolizumab 840 mg Q2W could be considered a safe starting dose and schedule. The dosing schedule used in this protocol is similar to the atezolizumab*

dosing schedule tested in previous clinical studies in patients with myeloid malignancies, such as relapsed/refractory and previously untreated AML and relapsed/refractory and previously untreated myelodysplastic syndrome (ClinicalTrials.gov Identifier: NCT02935361 and NCT02508870).

3.3.2 Rationale for Patient Population

Although the single-agent clinical activity of both atezolizumab and Hu5F9-G4 is limited in patients with advanced myeloid malignancies *(ORR of ≤10%),* preclinical exposure to Hu5F9-G4 is known to elicit a robust anti-tumor T-cell response. As such, in a sarcoma model, the combination of anti-CD47 (pro-phagocytic) and anti–cytotoxic T lymphocyte–associated protein 4 (anti–CTLA-4) (increased T-cell activation) antibodies results in decreased tumor growth and tumor regression compared with each used alone (refer to the Hu5F9-G4 Investigator's Brochure). In addition, PD assessment of bone marrow biopsies from patients with AML treated with Hu5F9-G4 demonstrated a significant increase in the bone marrow infiltrate of T cells, suggesting that sequential inhibition of CD47 signaling followed by blockade of PD-L1 may lead to clinical activity in patients with advanced myeloid malignancies.

The median T-cell population in bone marrow aspirates of patients with AML is 8%–25% (Daver et al. 2016). T cells make up a significantly larger proportion of the CD45-positive population (non-leukemic cells) in bone marrow aspirates from patients with AML compared with healthy donors (Daver et al. 2018). T cells in patients with AML exhibit distinct phenotypic and genotypic differences from T cells of healthy donors. The T cells in the bone marrow of patients with AML express activation markers (such as CD25, CD69, OX40) at a significantly higher rate than seen in healthy donors, indicating that the AML bone marrow is an inflamed microenvironment (Vidriales et al. 1993; Van den Hove et al. 1998). There is an increased overall expression of inhibitory surface molecules associated with T-cell exhaustion of CD4+ and CD8+ T cells in patients with AML compared with controls (Snorfeil et al. 2013; Daver et al. 2016; Tan et al. 2016). In addition, compared with healthy controls, patients with relapsed and newly diagnosed AML had a higher percentage of exhausted T-cell phenotype (PD-1+ TIM3+ and PD-1+ LAG3+ CD8 T cells) in the bone marrow (Williams et al. 2017). PD-1 expression on the T cells in bone marrow was higher in multiple-relapsed AML compared with first-salvage AML, newly diagnosed AML, or healthy donors (PD-1 on T cells in patients with multiple relapsed AML, which were greater than in patients receiving first salvage therapy and greater than in newly diagnosed patients, which were greater than in healthy donors), suggesting progressive T-cell exhaustion with more advanced-stage AML (Daver et al. 2016).

There are no approved treatments for patients with AML who are unable to achieve an initial CR or patients who relapse after initial response, with poor survival among this group of patients. Therefore, there is a high unmet medical need for new therapies for patients with R/R AML.

On the basis of these data, there is a strong preclinical and PD rationale for exploring the use of atezolizumab in combination with Hu5F9-G4 in patients with R/R AML. Finally, it is unclear why the PD-L1–positive immune-cell infiltrate present in the bone marrow of patients with AML and MDS is unresponsive to checkpoint modulation. Therefore, an unselected patient population will be enrolled in order to obtain samples for exploratory biomarkers of checkpoint resistance.

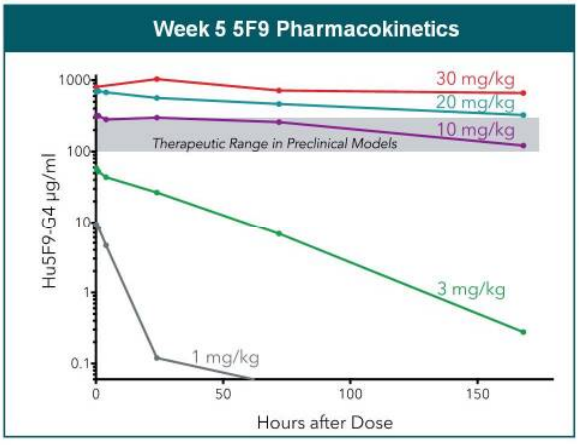
3.3.3 Rationale for Relapsed and/or Refractory AML

Between 10% and 40% of newly diagnosed patients with AML do not achieve CR with intensive induction therapy and are therefore categorized as having disease that is primary refractory or resistant. In addition, between 30% and 80% of patients who achieve a CR will subsequently relapse. Few of these patients can be cured with conventional salvage therapy (Thol et al. 2015). Most patients with R/R AML should be enrolled in clinical trials, given that highly effective and standardized treatments for AML are lacking and clinical trial enrollment is encouraged in this population.

3.3.4 Rationale for Hu5F9-G4 Dose

The dosing schedule chosen for Hu5F9-G4 was established during the Phase I clinical trial, during which no MTD was identified at doses of up to 30 mg/kg twice a week. In addition, PD assessments, conducted during the same Phase I clinical trial demonstrated that a priming dose for the first week, followed by escalating doses during the second week, and subsequently by weekly doses of the anti-CD47 monoclonal antibody, was not associated with early deaths, was safe and well tolerated in AML patients, resulted in a linear PK profile (see Figure 2), and optimal CD47 antigen binding in bone marrow at steady state (see Figure 2).

Figure 2 Hu5F9-G4 Achieves Target PK Levels at Clinically Feasible Doses



- 5F9 can overcome the CD47 antigen sink at 10 mg/kg or higher
- Antibody half-life is ~13 days
- Free plasma drug levels exceed preclinical activity thresholds identified from PK modeling (>100 to 250 µg/ml)

5F9 = Hu5F9-G4; PK = pharmacokinetic.
Source: Agoram et al. 2018.

3.3.5 Rationale for Pharmacokinetic Evaluation Schedule

The proposed sampling scheme for atezolizumab and Hu5F9-G4 concentration assessments will contribute to the characterization of study drug PK profiles in AML. Atezolizumab concentration results may be compared with single-agent data or available data from other atezolizumab clinical studies to assess whether there is any alteration in atezolizumab pharmacokinetics when co-administered with Hu5F9-G4 to patients with AML and to correlate any clinical activity and safety events.

The PK profile of Hu5F9-G4 will be characterized and may be compared with historical data to assess whether there is any alteration in PK properties when co-administered with atezolizumab. Based on the elimination pathways of the two molecules, PK interaction is not expected.

3.3.6 Rationale for Biomarker Assessments

Changes in immune-related biomarkers in blood and bone marrow may provide evidence for biologic activity of atezolizumab treatment combinations in humans and may allow for the development of a blood-based biomarker to help predict which patients may benefit from treatment with atezolizumab. In addition, these assessments may also highlight unique properties associated with resistance to checkpoint inhibitors in advanced myeloid malignancies. An exploratory objective of this study is to make a preliminary assessment of potential biomarkers associated with disease biology, mechanism(s) of action, potential mechanism(s) of resistance, pharmacodynamics, prognosis, and improvement of diagnostic assays.

Development of a predictive diagnostic assay that enables prospective identification of patients who are likely to respond to treatment with atezolizumab, alone or in combination with Hu5F9-G4, may allow for preselection of patients who are likely to benefit from treatment with these agents in future clinical studies.

Published results suggest that expression of PD-L1 in tumors (Herbst et al. 2014) and tumor immune cell infiltrates (Powles et al. 2014) correlate with response to anti–PD-1 therapy. In this study, AML specimens from patients who meet the eligibility criteria (see Sections 4.1.1 and 4.1.2) will be tested for PD-L1 expression (see Section 4.5.7.2 for sample requirements).

Other exploratory biomarkers, including potential predictive and prognostic markers that are related to response or clinical benefit of atezolizumab, tumor immunobiology, and tumor-type markers, may also be analyzed.

3.3.7 Rationale for Atezolizumab Treatment beyond Progression

Cancer immunotherapies may result in early apparent radiographic progression (pseudoprogression or tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009). Additionally, responding tumors may appear to increase in size because of the influx of immune cells (Hoos et al.

2010; Pennock et al. 2012). Unconventional response patterns have been described in patients treated with anti–CTLA-4 (Wolchok et al. 2009) and have been observed in the preliminary experience with atezolizumab in Study PCD4989g.

This has led to the use of modified Response Evaluation Criteria in Solid Tumors (RECIST) to account for potential pseudoprogression in clinical studies of atezolizumab in solid tumors. Tumor flare in patients with lymphoma and patients with chronic lymphocytic leukemia has been described in patients treated with lenalidomide (Eve and Rule 2010; Chanan-Khan et al. 2011). The clinical response has been studied in vitro and is believed to be a result of inhibition of B cell–receptor signaling and integrin $\alpha 4\beta 1$ adhesion of malignant cells to fibronectin and vascular cell adhesion protein 1. Although a similar tumor flare syndrome has not been described in the treatment of patients with AML or MDS, it is possible that such a phenomenon could occur. This could manifest itself as a decline in blood counts as a result of systemic or local cytokine release as a PD effect of treatment or T-cell infiltration of the bone marrow, leading not only to tumor killing but also to a bystander effect on normal bone marrow cells. Current response criteria for AML do not consider such observations, which is a phenomenon somewhat similar to the pseudoprogression described above in patients with solid tumors.

The decision to continue treatment beyond progression should be made between the patient and the investigator and should take into consideration the patient's wishes, clinical status, side effects experienced with study treatment, prognosis, and availability of other approved or experimental therapies. Treatment beyond progression also requires approval from the Medical Monitor. Patients who elect to receive treatment beyond progression will be required to sign a second copy of the original Consent Form and an Informed Consent Form for treatment beyond progression, depending on an institution's specific Institutional Review Board (IRB) requirements.

4. MATERIALS AND METHODS

4.1 PATIENTS

A maximum of 21 patients with R/R AML will be enrolled in this study. The planned enrollment for dose safety is between 6 and 12 patients, depending on the DLTs observed. Enrollment of the expansion cohort will range between 9 and 15 patients. The overall enrollment of this study will remain constant at 21 patients.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years at the time of signing Informed Consent Form
- Life expectancy of at least 12 weeks
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2 (see Appendix 4)

- Ability to comply with the study protocol, in the investigator's judgment
- Documented and confirmed R/R AML *per WHO* classification, except acute promyelocytic leukemia*, and lack of response to all therapies of known benefit*

  Refractory AML is defined as failure to attain a CR following exposure to at least two courses of intensive induction regimens, six cycles of single-agent HMA, or at least two cycles of venetoclax-containing regimens (combined to LDAC or HMAs).

  Relapsed AML is defined as the morphological detection of $\geq$5% bone marrow blasts, reappearance of leukemic blasts in the blood, or development of extramedullary disease. For patients previously found to be in CR and minimal residual disease (MRD) negative (by flow cytometry), reappearance of a leukemic population by MRD testing can be classified as being relapsed AML (conversion from CR MRD negative to CR MRD positive).
- Adequate end-organ function, defined using the following laboratory parameters obtained within 28 days prior to the first dose of study drug:
  - AST, ALT, and ALP $\leq 2.5\times$ upper limit of normal (ULN)
  - Serum bilirubin $\leq 2\times$ ULN, with the following exception:

    Patients with known Gilbert disease or clear evidence of transfusion-related hemolysis who have serum bilirubin $\leq 3\times$ ULN may be enrolled. Cases of transfusion-related hemolysis must be discussed and approved by the Medical Monitor.
  - Serum creatinine $\leq 2\times$ ULN
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA $<$500 IU/mL at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- WBC count $\leq 20\times 10^3/\mu$L prior to the first dose of study treatment and prior to each Hu5F9-G4 dose for Cycle 1

  Patients with WBC $>20\times 10^3/\mu$L can be treated with hydroxyurea throughout the trial to reduce the WBC to $\leq 20\times 10^3/\mu$L.
- Willingness and ability to provide pretreatment bone marrow aspirate and biopsy and agreement to provide subsequent bone marrow aspirates and biopsies during study treatment

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

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab and/or Hu5F9-G4, whichever is longer. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (tubal ligation, removal of ovaries and/or uterus).

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$per year during the treatment period and for at least 120 days after the final dose of atezolizumab and/or Hu5F9-G4. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 60 days after the final dose of atezolizumab and/or Hu5F9-G4 to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile: requirement for a negative serum pregnancy test result within 14 days prior to initiation of study treatment

4.1.2 Exclusion Criteria

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

- Previous allo-HSCT within 6 months prior to enrollment, active graft versus host disease, or requiring transplant-related immunosuppression
- Prior solid organ transplant
- Evidence of active CNS involvement by leukemia

  Patients with a history of leukemic CNS involvement that has been treated may have to undergo lumbar puncture and/or magnetic resonance imaging assessment prior to study entry at the discretion of the Medical Monitor.
- Pregnancy or lactation or intention to become pregnant during the study or within 5 months after the final dose of atezolizumab and/or Hu5F9-G4, whichever is longer

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- History of idiopathic pulmonary fibrosis, organizing pneumonitis (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis
- History of autoimmune disease

  Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement may be eligible for this study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen may be eligible for this study.

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

  - Rash must cover $<10\%$ of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  - No occurrence of acute exacerbations of the underlying condition that require psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- Treatment with investigational therapy within 14 days prior to initiation of study drug
- Any approved AML-related therapy within 14 days prior to enrollment

  Granulocyte colony-stimulating factor (G-CSF) to treat neutropenic fever and/or infection is permitted.

  Hydroxyurea may be used throughout the trial to control peripheral blood blast counts in response to the first dose of study treatment.

- Immunosuppressive therapy (including, but not limited to, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and anti–necrosis factor [anti-TNF] factor agents) within 6 weeks of Day 1 of Cycle 1
- Daily requirement for corticosteroids (> 10 mg/day prednisone or equivalent, except for inhalation corticosteroids) within 2 weeks prior to Day 1 of Cycle 1
- Prior treatment with immune checkpoint blockade therapies (anti–CTLA-4, anti–PD-1 or anti–PD-L1) or immune agonists (anti-CD137, anti-CD40, and anti-OX40) or immune antagonists (anti-CD47)
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α and interleukin [IL]-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to Day 1 of Cycle 1
- Treatment with denosumab (or other RANKL inhibitor) 4 weeks before the first dose and for 10 weeks after the final dose of atezolizumab

  Patients receiving denosumab therapy must be willing to be treated with a bisphosphonate while receiving study treatment.
- Administration of a live, attenuated vaccine within 4 weeks of Day 1 of Cycle 1 or anticipation that such a live, attenuated vaccine will be required during the study or within 5 months after the final dose of atezolizumab

  Influenza vaccination should be given during influenza season only (approximately October through May in the northern hemisphere and approximately April through September in the southern hemisphere). Patients must agree not to receive live, attenuated vaccines (e.g., FluMist®) within 28 days prior to enrollment, during treatment, or within 5 months following the final dose of atezolizumab.
- Planned major surgery during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Poor peripheral venous access, unless prior central venous catheter placement has been performed
- Active infection

  Patients being treated for non-serious infectious complications (e.g., oral candidiasis or uncomplicated urinary tract infection) with oral or topical antimicrobials may be eligible for study treatment (antimicrobial treatment must be completed prior to Day 1 of Cycle 1 and cases must be discussed and approved by the Medical Monitor).

- Severe infection requiring hospitalization or IV antibiotics within 14 days prior to enrollment

  Patients receiving prophylactic antibiotics, antifungals, and antivirals as a result of prolonged neutropenia in the absence of active documented infection are eligible.

  Patients receiving IV antibiotics and hospitalization for febrile neutropenia may be eligible, if initial diagnosis of neutropenic fever was not due to any infectious etiology and the patient has been afebrile for $\geq$72 hours.
- Any serious medical condition or abnormality in clinical laboratory test results that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History or presence of an abnormal ECG finding that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, and evidence of prior myocardial infarction
- History of other malignancy within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS of $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells or any component of the atezolizumab, azacytidine, or Hu5F9-G4 formulation
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known allergy or hypersensitivity to any component of the atezolizumab and/or Hu5F9-G4 formulation

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study.

Enrollment tracking will be performed through the use of the interactive voice or web-based response system (IxRS). Prior to initiation of screening, the study site personnel should confirm through the appropriate communication channel that the safety or expansion cohort is open for enrollment. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's *review prior* to *enrollment of* the patient. Once the Sponsor reviews a patient for enrollment, a patient number will be assigned and the patient will be enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening for a particular disease cohort.

The first 6 patients with relapsed AML will be assigned to the safety cohort. Once these patients are fully assessed and deemed to be safely tolerating the study treatment, an additional 15 patients with R/R AML will be enrolled in the expansion cohort as shown in Figure 1.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and Hu5F9-G4.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

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

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

4.3.1.2 Hu5F9-G4

Hu5F9-G4 is a sterile, clear, to slightly opalescent, colorless, preservative-free liquid for IV administration. Hu5F9-G4 drug product is supplied by the Sponsor at a concentration of 20 mg/mL in 200-mg (10-mL) single-use, type 1 borosilicate glass vials with butyl rubber stoppers and aluminum seals. The product is formulated for IV administration in 0.01% (w/v) polysorbate 20, 5% (w/v) sorbitol, and 10 mM sodium acetate, at pH 5.0, and Sterile Water for Injection. Each product vial is intended to deliver 10 mL of drug solution (200 mg of Hu5F9-G4). Saline for infusion will be used as the diluent for final dosage preparation.

Hu5F9-G4 is shipped refrigerated and must be stored at 2°C–8°C (36°F–46°F) until use, with access limited to pharmacy personnel, the Principal Investigator, or a duly designated person. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, the Sponsor should be contacted.

Recommended safety measures for preparation and handling of Hu5F9-G4 include laboratory coats and gloves. In addition, Hu5F9-G4 cannot be mixed with any other drug in the infusion bag or administration. Hu5F9-G4 should not be administered as a bolus injection.

Hu5F9-G4 should be protected from light. Sufficient protection from light is provided by the secondary container. No specific light protection is needed during preparation of the dosing solution and infusion.

Hu5F9-G4 is not formulated with a preservative. Therefore, once the sterile vials are entered, all dose preparations should be performed aseptically. The infusion of the drug should be completed within 8 hours of preparation of the solution.

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab

The dose level of atezolizumab in this study is 840 mg administered to patients by IV infusion on Days 8 and 22 of each 28-day cycle (Q2W) for patients enrolled in the safety cohort and in the expansion cohort. During the first cycle of treatment (Cycle 1), patients will receive 840 mg IV atezolizumab only on Day 22 in order to collect bone marrow and blood samples for biomarker assessment after steady state has been reached for Hu5F9-G4.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Administration of 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. For anaphylaxis precautions, see Appendix 7. Atezolizumab and Hu5F9-G4 infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab and Hu5F9-G4 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. • *For the first **two** doses of atezolizumab following Hu5F9-G4, at least 60 minutes should be allowed for observation after Hu5F-G4 administration and 60 minutes for observation after atezolizumab administration.* • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • *If no infusion-associated adverse events are observed during the initial two combination treatment sessions, a 30-minute observation period between Hu5F9-G4 and atezolizumab infusion and a 30-minute observation period after atezolizumab infusion could be considered for subsequent administrations.*

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

Guidelines for medical management of IRRs are provided in the Appendix 8.

4.3.2.2 Hu5F9-G4

The initial priming dose will be administered as a continuous IV infusion in 250 mL of normal saline over 180 minutes to reduce the risk of acute hemagglutination. All other infusions for doses >1 mg/kg will be administered in 500 mL over 120 minutes. If more than 4 weeks have elapsed since the last dose of Hu5F9-G4 and the patient is to resume treatment, patients must undergo intra-patient dose escalation again of Hu5F9-G4 based on their original dosing regimen (e.g., 1 mg/kg of priming dose on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Days 11, 15, and 22).

The dose level of Hu5F9-G4 administered to patients by IV infusion in this study varies according to the week of treatment. Initially, two priming doses of 1 mg/kg will be given on Days 1 and 4 of Cycle 1. This will be followed by loading doses of 15 mg/kg on Day 8, followed by 30 mg/kg on Day 11 of Cycle 1. Starting on Day 15, Hu5F9-G4 maintenance will be given at a dose of 30 mg/kg QW.

Premedication is required before administration of the first four doses of Hu5F9-G4 with 650–1000 mg of oral acetaminophen and 25–50 mg of oral or IV diphenhydramine or comparable regimen.

Recommended safety measures for preparation and handling of Hu5F9-G4 include laboratory coats and gloves. In addition, Hu5F9-G4 cannot be mixed with any other drug in the infusion bag or administration. Hu5F9-G4 should not be administered as a bolus injection.

There have been no late-onset hypersensitivity reactions. Thus, recommendations for potential infusion reactions should follow recommendations from Table 2 (see Section 4.3.2.1). Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 8.

4.3.3 Investigational Medicinal Product Accountability

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 (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Post-Study Access to Atezolizumab and Hu5F9-G4

Currently, Sponsor does not have any plans to provide Roche IMPs (atezolizumab and Hu5F9-G4) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab and Hu5F9-G4 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

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, vaccines, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to screening to the study completion or treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Prophylactic use of oral antibiotics, anti-viral medications, and anti-fungal medications for prolonged neutropenia according to the following guidelines:
  - Mandated use of anti-microbial prophylaxis (fluoroquinolone) for all patients enrolled in the study until 4 weeks following documentation of CR (CR or CRi) is documented:

    Oral levofloxacin (500 mg daily)

    Oral ciprofloxacin (500 mg orally [PO] twice daily)

    A third generation cephalosporins (e.g., cefotaxime, cefixime, ceftazidime, cefpodoxime, ceftriaxone, cefdinir, cefoperazone, ceftibuten, moxalactam, ceftizoxime)

    Other recommended antibiotic prophylaxis routinely preferred by the investigator or based on institutional guidelines
  - Mandated use of anti-fungal prophylaxis for patients with ANC $<500/\mu L$ at any time during the study and until 4 weeks following documentation of a CR (CR or CRi):

    Posaconazole: oral suspension 200 mg (5 mL) PO three times daily or tablet 300 mg PO twice daily on Day 1, followed by 300 mg PO daily

    Voriconazole: 200 mg PO twice daily

    Isavuconazonium sulfate (Cresemba®): 180 mg PO (two capsules every 8 hours for six doses followed by two capsules once daily)

    Other recommended anti-fungal prophylaxis routinely preferred by the investigator or based on institutional guidelines

- Mandated use of anti-viral prophylaxis for patients with ANC $< 500/\mu L$ at any time during the study and until 4 weeks following documentation of CR (CR or CRi):

  Acyclovir: 400 mg once daily or 200 mg twice daily

  Valacyclovir: 500 mg or 1,000 mg orally every 8 hours

  Other recommended anti-viral prophylaxis routinely preferred by the investigator or based on institutional guidelines

- The use of G-CSF to treat a documented or suspected infection associated with febrile neutropenia
- Anti-emetic therapy, in accordance with institutional guidelines, is allowed for supportive-care purposes.
- Systemic corticosteroids, tocilizumab, and TNF-α inhibitors

  In the event of severe systemic IRRs or systemic inflammatory activation, the Medical Monitor should be notified as soon as possible after the patient has been treated. Systemic corticosteroids, tocilizumab, and TNF-α inhibitors may attenuate potential beneficial immunological effects of treatment with atezolizumab but may be administered for moderate immune-mediated adverse events at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered.

- For males and females of reproductive potential, highly effective means of contraception (see Section 4.1.1)

Premedication with antihistamines, anti-pyretic medicines, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. For patients achieving a CR (CR, CRi, CRp, or CRh), prophylactic anti-infective therapy, including antibiotic, anti-viral, and anti-fungal therapy can be discontinued, at the discretion of the investigator, no earlier than 30 days from documentation of CR. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

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

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 9 for details).

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited. This includes, but is not limited to, the following:

- Erythropoietin-stimulating agents within 2 weeks of Day 1 of Cycle 1
- G-CSF solely to maintain ANC and not associated with the treatment of a documented or suspected infection in the setting of febrile neutropenia
- Concomitant therapy intended for the treatment of cancer whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.

  Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug–drug interactions that may cause or confound assessment of toxicity.
- Investigational therapy is prohibited within 14 days prior to initiation of study treatment and during study treatment.
- Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

The following therapies are excluded while patients are receiving atezolizumab and for 10 weeks after the final dose of atezolizumab:

- Patients who are receiving a RANKL inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead; denosumab could potentially alter the activity and the safety of atezolizumab.
- Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon-α (IFN-α), IFN-γ, or interleukin-2 (IL-2). These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

  Patients should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Patients should not receive immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, and methotrexate. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti–TNF-α agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.
- Patients must not receive live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to Day 1 of Cycle 1, at any time during the study, or within 5 months following the final dose of atezolizumab. Inactivated vaccines are allowed.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. The schedule for PK and immunogenicity sample collection is presented in Appendix 2, and the biomarker sample collection is provided in Appendix 3. All activities must be performed and documented for each patient.

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

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

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

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

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. A complete physical examination is required during screening, on Day 1 of every cycle of treatment beyond Cycle 1 and at the end of treatment, and every 3 months during follow-up prior to progression (see Appendix 1).

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

Height and weight should be recorded at specified timepoints (height to be measured only at screening).

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs (including resting, blood oxygen saturation measured by pulse oximetry) will be recorded during screening. Vital signs (not including pulse oximetry) will be measured prior to every injection of Hu5F9-G4. After Hu5F9-G4 administration, vital sign monitoring is not required unless clinically indicated. The patient's vital signs should be recorded up to 60 minutes prior to each atezolizumab infusion (see Table 3). Vital signs should also be recorded during or after the atezolizumab infusion if clinically indicated. Additional vital sign measurements should be obtained per the specified timepoints in Appendix 1.

Blood oxygen saturation by pulse oximetry (while the patient is resting) should also be determined within 60 minutes before the first dose of atezolizumab.

Table 3 Timing for Vital Sign Measurements for First and Subsequent Infusions

	Timing for Vital Sign Measurements	
Study Drug	First Infusion	Subsequent Infusions
Hu5F9-G4	• Measure within 60 minutes prior to the atezolizumab infusion. • Record patient's vital signs during or after the infusion if clinically indicated.	• Measure within 60 minutes prior to the atezolizumab infusion. • Record patient's vital signs during or after the infusion if clinically indicated.
Atezolizumab	• See Table 2 for guidelines.	• See Table 2 for guidelines.

4.5.5 ECOG Performance Status

Performance status will be assessed using the ECOG Performance Status Scale and recorded on the eCRF (see Appendix 4).

4.5.6 AML and Response Evaluations

Any evaluable or measurable disease must be documented at screening and re-assessed at each subsequent cancer evaluation. Patients should have AML evaluation and classification based on the 2010 ELN and 2017 ELN criteria (see Appendix 5). Disease prognosis should also be classified at screening using the modified ELN risk classification (see Appendix 5). Responses will be assessed by the investigator through use of the ELN recommendations (see Appendix 5).

Bone marrow examinations must include aspirate and biopsy (whenever possible) for morphology, flow cytometry, and routine cytogenetic and are required at screening. If fluorescence in situ hybridization (FISH) is performed at screening, FISH must be

performed during subsequent assessments. Refer to Section 4.5.7.2 for timepoints and requirements regarding collection of required bone marrow samples (aspirates and trephine/core biopsies) for exploratory biomarker studies. Bone marrow aspirates and biopsies are to be performed on Day 22 of Cycle 1 and subsequently after 3 and 6 months of study treatment (i.e., Day 1 of Cycles 4 and 7; see Appendix 1). Beyond 6 months of study treatment, bone marrow aspirates are required within 7 days prior to study drug administration on Day 1 of every 3 months (i.e., Day 1 of Cycles 10, 13, 16, etc.) (for determination of response), at the time of relapse or progressive disease, and at the end of treatment. For patients in follow-up who discontinue study treatment prior to disease progression, bone marrow aspirates and biopsy should be collected every 4 months (see Appendix 1). All bone marrow examinations should be assessed locally (see Section 4.5.3). Local institutional policies should be followed at any other time during the study when a bone marrow examination is deemed necessary by the investigator.

In addition, information on transfusion requirements prior to and during study treatment will also be collected (see Appendix 1).

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistry panel, virology, coagulation, and pregnancy will be analyzed at the study site's local laboratory. Central laboratories will coordinate the collection of fresh bone marrow and blood samples for the assessment of atezolizumab and Hu5F9-G4 pharmacokinetics and biomarkers, ADA assays, and autoantibody testing. Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.7.1 Local Laboratory Assessments

Local laboratory assessments will include the following:

- Hematology: CBC, including RBC count, hemoglobin, hematocrit, WBC with differential count (i.e., neutrophils [bands are optional], lymphocytes, eosinophils, basophils, and monocytes), reticulocytes, platelet count, and circulating peripheral blasts
- Serum chemistry panel: glucose (while patient is fasting at baseline), BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, LDH, creatine kinase, uric acid, and total protein
- Bone marrow aspirate and trephine biopsy for response assessment (morphology, flow cytometry, cytogenetics, and FISH [if applicable])
- Coagulation: aPTT or PTT and INR
- Thyroid-function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)

- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

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

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

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

- Epstein-Barr viral serology (IgG and IgM)
- HIV serology: All patients will be tested for HIV prior to inclusion into the study, and patients who are HIV positive will be excluded from the study.
- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at subsequent visits if clinically indicated. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

4.5.7.2 Central Laboratory Assessments

The following assessments will be performed at a central laboratory or by the Sponsor:

- Serum PK samples

  Samples will be assayed for the presence of ADAs to atezolizumab and Hu5F9-G4 with the use of validated immunoassays.

- Biomarker assays in blood and bone marrow samples

Blood samples will be obtained for biomarker evaluation (including, but not limited to, biomarkers that are related to AML or cancer immune biology) from all eligible patients according to the schedule in Appendix 3. Samples will be processed to obtain plasma for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and/or DNA).

Fresh bone marrow aspirates and trephine biopsies with the associated pathology report must be collected for biomarker analysis at screening, during treatment, at the end of treatment, and at the time of disease relapse, progression, and/or suspected progression as outlined in Appendix 3. Leftover tissue from unscheduled bone marrow aspirate and biopsies (performed per the investigator's discretion for clinical reasons) should also be collected for biomarker analysis.

- For bone marrow aspirate samples, up to 10 mL of aspirate should be collected. Preferably, the same aspirate site used for collection of local bone marrow laboratory samples (e.g., flow cytometry, cytogenetics, FISH) should not be used for collection of bone marrow aspirate samples for exploratory analyses. For every 10 mL of bone marrow collected, a separate aspirate site should be selected (all aspirate sites can be on the ipsilateral iliac crest), if possible.
- Trephine/core biopsy tissue samples preferably should be a minimum of 1.5 cm in length and ≥2 cm is optimal. Newly collected tissue should be shipped to a central laboratory for decalcification and processing (preferred). If fresh tissue cannot be submitted, tissue blocks or 15–20 newly serially sectioned, unstained slides of trephine/core biopsy samples should be sent to the appropriate central laboratory (see the laboratory manual for further details).

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, bone marrow aspirate, bone marrow biopsy samples, and their derivatives (e.g., DNA, RNA) samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4. When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Screening blood, tumor tissue, and bone marrow aspirate samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 4. Biomarker samples may also be used for additional method development, assay validation, and characterization. Given the complexity and exploratory nature of biomarker analyses, results from the analyses will not be shared with investigators or study participants, unless required by law.

Table 4 Proposed Exploratory Biomarkers

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Plasma	Baseline and subsequent timepoints during treatment	• Cytokine levels
RNA/DNA extracted from blood	Baseline and subsequent timepoints during treatment	• Transcriptome profiling and gene expression profiling • Mutational profiling • TCR cloning
Peripheral blood	Baseline and subsequent timepoints during and after treatment	• Frequency of immune cell populations and CIT markers
Bone marrow aspirate	Baseline and subsequent timepoints during and after treatment	• Frequency of immune cell populations and CIT markers • PD-L1 and CD47 expression • Cytokines
RNA/DNA extracted from bone marrow aspirate/biopsy	Baseline and subsequent timepoints during and after treatment (time of progression)	• Mutational profiling • MRD • Transcriptome profiling and gene expression profiling • TCR cloning
Bone marrow biopsy	Baseline and subsequent timepoints during and after treatment	• IHC for immune cells • Gene expression profiling

CIT = cancer immunotherapy; IHC = immunochemistry; MRD = minimal residual disease; TCR = T-cell receptor.

Refer to the laboratory manual for additional details on laboratory assessments and sampling.

4.5.8 Electrocardiograms

Single 12-lead ECG recordings will be obtained during screening and during the study if clinically indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

If at a particular postdose timepoint, the mean QT interval corrected through use of Fridericia's formula (QTcF) is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

4.5.9 Evaluation of Left Ventricular Ejection Fraction

Left ventricular ejection fraction will be by measurement of ejection fraction using echocardiogram or multiple-gated acquisition scan at screening and during the study if clinically indicated.

4.5.10 Anti-Drug Antibody Testing

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening, confirmatory, and titer assays will be employed to detect ADAs at multiple timepoints before, during, and after treatment with atezolizumab and Hu5F9-G4 (see Appendix 2 for the schedule of ADA assessments). ADA response will be correlated with relevant clinical endpoints to understand its clinical significance. Additional ADA assays (e.g., neutralizing antibody assay) may be employed to further characterize ADA response.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

4.5.11.2 Approval by the Institutional Review Board

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.6) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to the investigational agents, disease, or drug safety:

- Blood sample collected on Day 1 of Cycle 1
- Leftover blood, serum, plasma, PBMCs, and tumor tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., biopsies for extramedullary sites of disease), performed at the investigator's discretion during the study

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

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

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

RBR samples are to be stored no later than 15 years after the final Clinical Study Report has been completed. However, the RBR storage period will be in accordance with the IRB-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

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

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

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

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

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.11.6 Withdrawal from the Research Biosample Repository

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

global_rcr-withdrawal@roche.com

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

4.5.11.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and Hu5F9-G4) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of PBMC and/or bone marrow biopsy data and clinical status (e.g., symptomatic deterioration such as worse cytopenias) (see Section 3.1.1 for details)

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

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Inaccurate or incomplete data recording

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

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice and country or local regulations.
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and Hu5F9-G4 in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 and 5.1.2).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and Hu5F9-G4 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 treatment interruption or discontinuation, are provided in Appendix 8 and Appendix 9. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Administration of atezolizumab and Hu5F9-G4 will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded during the study and for up to 30 days after the final dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first. The potential safety issues anticipated in this study and measures intended to avoid or minimize such toxicities are outlined in the following sections.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage

activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Hu5F9-G4

Hu5F9-G4 has been associated with risks such as the expected effects of anemia and hemagglutination in patients with solid tumors and AML who have been treated with Hu5F9-G4 and are consistent with preclinical toxicology studies. Use of a priming and maintenance dose appears to mitigate the acute hematological effects of Hu5F9-G4. Mostly mild to moderate IRRs (fevers, chills, headache, and other symptoms) have occurred generally with the first few doses of Hu5F9-G4 and are well managed with premedications. Overall, the majority of Hu5F9-G4–associated toxicities observed to date have been transient and manageable. Supportive care with frequent RBC and platelet transfusions has been safely and successfully administered to patients receiving Hu5F9-G4 therapy.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Hu5F9-G4

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and Hu5F9-G4: pulmonary, hepatic, gastrointestinal, endocrine, ocular, cardiac, dermatologic, neurologic, meningoencephalitis, renal events, myositis, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome. Both atezolizumab and Hu5F9-G4 are known to cause IRRs and anemia. It is not known the synergistic effects of combination therapy on the known adverse event profile of single-agent treatment.

5.1.4 Dose Modifications for Hu5F9-G4 and Atezolizumab

See Appendix 8 for guidance on dose modification for atezolizumab and Hu5F9-G4.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)

- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, and toxic epidermal necrolysis)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

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

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of R/R AML should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Acute Myeloid Leukemia

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on IWG 2003 and 2017 ELN recommendations (Döhner et al. 2017). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

5.3.5.12 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. 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 Section 5.4.2). For atezolizumab and Hu5F9-G4, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with atezolizumab and Hu5F9-G4, 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.

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.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information in North America

Medical Monitor/Roche Medical Responsible: [redacted], M.D. (primary)

E-mail: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Email: [redacted]

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide

medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing

the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 120 days after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site's IRB, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest defined as 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

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

- Atezolizumab Investigator's Brochure
- Hu5F9-G4 Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis will be based on patient data collected through study discontinuation or the end of study. All analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of either study drug.

6.1 DETERMINATION OF SAMPLE SIZE

Design considerations covering all cohorts were not made with regard to explicit power and type I error considerations but to obtain preliminary safety, efficacy, PK, and PD information on atezolizumab in combination with Hu5F9-G4. The planned enrollment for this study is 21 patients, depending on the safety profile observed during the safety evaluation phase. The study will enroll approximately 6 patients in the safety cohort and approximately 15 patients in the expansion cohort. The sample size may increase as a result of dose findings. The probabilities of observing adverse events in at least 1 patient, given the varying actual adverse event rates, are listed in Table 6.

Table 7 Probability of Safety-Signal Detection with a Cohort of 21 Patients

True Underlying Probability of an Adverse Event	Probability of Observing at Least One Adverse Event in 20 Patients (%)
0.01	19.0
0.025	41.2
0.05	65.9
0.075	80.5
0.1	89.1

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations, and discontinuations from the study will be summarized descriptively by the assigned dose, schedule, and cohort.

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics such as age, sex, weight, duration of malignancy, and baseline ECOG Performance Status will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented for the overall cohort.

Study drug administration data will be listed by dose and schedule and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose of atezolizumab and Hu5F9-G4 received.

6.4 SAFETY ANALYSES

The safety analyses will include all patients who receive any amount of either study drug, with patients grouped as a whole.

Safety will be assessed through summaries of adverse events, change from baseline in targeted vital signs, laboratory test results, and physical examination findings.

All collected adverse event data will be listed by assigned dose level and patient number. All adverse events occurring on or after treatment on Day 1 of Cycle 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. DLTs and adverse events leading to treatment discontinuation will also be listed separately.

6.5 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of all subjects with at least one PK value that can be reported. As appropriate, serum concentrations of atezolizumab and Hu5F9-G4 will be tabulated, summarized, and plotted after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modeling, including pooled analyses across studies)

may also be performed as appropriate. If performed, these additional analyses may be reported separately from the clinical study report. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of the study treatments administered. Depending on the results from interim PK analyses, the frequency of PK sampling may be reduced later in the study.

6.6 EFFICACY ANALYSES

Response assessment data (ORR, DOR, EFS, LFS, OS, PFS, the rate of transfusion independence, and the duration of transfusion independence) will be summarized for all patients as a single cohort. Time-to-event data will be summarized using Kaplan-Meier methods.

Interim looks may be performed during the study. Response data will be compared with the comparable historical data using statistical methodology such as a predictive and/or posterior probability design (Lee and Liu 2008), with the modification that the uncertainty in the historical control data is fully taken into account by utilizing a distribution on the control response rate to enable internal decision-making for future development. The possible data sources to be used as historical controls may be publications, real-world data sources, and other reliable information on efficacy from other studies in similar patient groups that will be available by the time of the interim analysis.

6.6.1 Primary Efficacy Endpoint

Primary efficacy endpoints include CR rate (CR + CRp + CRi + CRh) and DOR.

The CR rate will be assessed as the percentage of patients who achieve a CR, CRp, CRi, or CRh (as defined by the IWG 2003 and ELN 2010 criteria) after up to six cycles of combination therapy. The CR rate will be estimated, and the 95% confidence interval will be calculated.

DOR will be analyzed for the subset of patients who achieve an objective response as defined in Section 2.3.1. DOR is defined as the time from the initial response to the time of disease progression or death (whichever occurs first). If a patient is alive and has not experienced progressive disease before the end of the study, DOR will be censored at the day of the last cancer assessment. If no cancer assessments are performed after the date of the first occurrence of an objective response, DOR will be censored at the date of the first occurrence of an objective response plus 1 day.

6.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include ORR, EFS, LFS, PFS, OS, the rate of transfusion independence, and the duration of transfusion independence (see Section 2.3.2), which will be analyzed as follows:

- ORR will be assessed as the proportion of patients who obtain a CR, CRp, CRi, CRh or PR (as defined by the IWG 2003 and ELN 2010) after up to six cycles of combination therapy. The proportions will be calculated for categorical variables by dividing the number of patients with a positive response by the number of patients. Patients with no response assessments (for whatever reason) will be considered non-responders.
- For EFS, data from patients not known to have any of the listed events will be censored on the date they were last examined. For patients who do not achieve a CR, CRp, CRh, or CRi, EFS is defined as the point of progression or death, whichever comes first.
- For LFS, data from patients not known to have any of these events will be censored on the date they were last examined.
- For OS, data for patients who did not die will be censored at the date of last study visit or the last known date to be alive, whichever is later. If no postbaseline data are available, OS will be censored at the date of first treatment plus 1 day.
- Rate of transfusion independence is defined as the proportion of patients who achieve transfusion independence at any time during study treatment. Transfusion independence is defined as achieving any continuous 56-day window without requiring platelet or RBC transfusions.
- Duration of transfusion independence is defined as the number of consecutive days of transfusion independence, measured from 1 day after last transfusion to disease progression or subsequent transfusion.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not

have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

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

6.8 BIOMARKER ANALYSES

The exploratory data generated with the use of fresh cancer tissues and/or blood samples (see Section 4.5.7.2) may be listed by patient, dose, cohort, and response status. In addition, the relationships between these data and observed safety or clinical activity may be assessed.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper patient-reported data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of

the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the clinical study report has been completed or for the length of time required by relevant medical or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC and General Data Protection Regulation as applicable) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

Patients 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 policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD

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

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

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

other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 6–10 sites globally will participate and enroll approximately 21 patients. The planned enrollment for dose safety is between 6 and 12 patients, depending on the DLTs observed. Enrollment of the expansion cohort will range between 9 and 15 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.3.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will

comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

Assessment/Procedure	Screening	Treatment Cycles (28-Day Cycles)		Treatment Discontinuation [a]	Survival Follow-Up
		Cycle 1	(Cycle 2 and Beyond)		
	Days –28 to –1	Day 1 (±3 days)	Day 1 (±3 days)	≤30 Days after Final Dose	
Informed consent	x [b]				
Baseline bone marrow sample [c]	x				
Demographic data (sex, race/ethnicity, and age)	x				
Medical history and baseline conditions	x				
Transfusion history	x				
Transfusion record		x	x	x	
Type and screen (ABO/Rh), DAT, and RBC phenotyping	x				
ELN risk classification	x				
Vital signs and pulse oximetry [d]	x	x [g]	x	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination [e]	x		x	x	
Limited physical examination [f]		x			
ECOG Performance Status	x	x	x	x	
12-Lead ECG [g]	x	Perform if clinically indicated.			
ECHO or MUGA scan [h]	x	Perform if clinically indicated.			

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure	Screening	Treatment Cycles (28-Day Cycles)		Treatment Discontinuation [a]	Survival Follow-Up
		Cycle 1	Maintenance Cycles 2 and Beyond		
	Days –28 to –1	Day 1 (±3 days)	Day 1 (±3 days)	≤30 Days after Final Dose	
Hematology [i]	x [j]	x [k]	x	x	
Serum chemistry panel [l]	x [j]	x [k]	x	x	
Pregnancy test [m]	x [j]		x	x	
Coagulation: aPTT or PTT and INR	x [j]			x	
Thyroid-function testing: TSH, free T3 (or total T3), and free T4 [n]	x [j]	x [n]		x	
Viral serology	x [j, o]		x [p]	x [p]	x [p]
Urinalysis [q]	x [j]	Perform if clinically indicated. [r]			
Atezolizumab PK sample		See Appendix 2 for sampling schedule.			
Hu5F9-G4 PK sample		See Appendix 2 for sampling schedule.			
ADA sample		See Appendix 2 for sampling schedule.			x
Plasma and whole blood samples for biomarkers	See Appendix 3 for sampling schedule.				
Blood sample (for DNA isolation) for RBR (optional) [s]		x			

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure	Screening	Treatment Cycles (28-Day Cycles)		Treatment Discontinuation [a]	Survival Follow-Up
		Cycle 1	Cycles 2 and Beyond		
	Days –28 to –1	Day 1 (±3 days)	Day 1 (±3 days)	≤30 Days after Final Dose	
Bone marrow biopsy and aspirate for biomarker assessment	See Appendix 3 for sampling schedule.				
Tumor response assessments	x	x [t]			
Concomitant medications [u]	x [u]	x	x	x	
Adverse events [v]	x [v]	x [v]	x	x	x [u]
Hu-5F9-G4 administration [w]		x [w]	x [w]		
Atezolizumab administration		x [x]	x [x]		
Survival follow-up and anti-cancer treatment					x [y]

ADA = anti-drug antibody; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ELN = European LeukemiaNet; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA = multiple-gated acquisition (scan); PK = pharmacokinetic; Q2W = every 2 weeks; QW = once a week; QTcF = QT interval corrected through use of Fridericia's formula; RBR = Research Biosample Repository; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

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

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

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

[c] A pretreatment bone marrow aspirate and biopsy are required.

[d] Vital signs will include measurement of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs (including resting, blood oxygen saturation measured by pulse oximetry) will be recorded during screening. Vital signs (not including pulse oximetry) will be measured prior to every injection of Hu5F9-G4. After Hu5F9-G4 administration, vital sign monitoring is not required unless clinically indicated. The patient's vital signs should be assessed up to 60 minutes prior to each atezolizumab infusion (see Table 2). Vital signs should also be recorded during or after the atezolizumab infusion if clinically indicated. Blood oxygen saturation, as measured by pulse oximetry (while the patient is at rest), should also be determined within 60 minutes before the first dose of atezolizumab.

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Single 12-lead ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to when other procedures are scheduled at the same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. If at a particular post-dose timepoint, the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator.

[h] Performed at screening and as clinically indicated.

[i] Hematology includes CBC, including RBC count, hemoglobin, hematocrit, WBC with differential count (i.e., neutrophils [bands are optional], lymphocytes, eosinophils, basophils, and monocytes), reticulocytes, platelet count, and circulating peripheral blasts.

[j] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 24 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Serum chemistry panel includes glucose (while patient is fasting at baseline), BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate (or total carbon dioxide (if considered standard of care for the region) calcium, phosphorus, albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, LDH, creatine kinase, uric acid, and total protein.

[m] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at subsequent visits if clinically indicated. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every three cycles thereafter (i.e., Cycles 4, 7, 10, etc.).

[o] At screening, patients will be tested for HIV, HBsAg, total HBcAb, HBV antibody, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection. Epstein-Barr viral serology (IgG and IgM) will also be performed.

[p] Patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests every 3 months (± 7 days) during treatment, at treatment discontinuation (± 7 days), and at 3, 6, 9, and 12 months (± 14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥ 500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

Appendix 1
Schedule of Activities (cont.)

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

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

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

[t] Bone marrow examinations must include aspirate and biopsy (whenever possible) for morphology, flow cytometry, and routine cytogenetic and are required at screening. If fluorescence in situ hybridization (FISH) is performed at screening, FISH must be performed during subsequent assessments. Refer to Section 4.5.7.2 for timepoints and requirements regarding collection of required bone marrow samples (aspirates and trephine/core biopsies) for exploratory biomarker studies. Bone marrow aspirates and biopsies are to be performed on Day 22 of Cycle 1 and subsequently after 3 and 6 months of study treatment (i.e., Day 1 of Cycles 4 and 7). Beyond 6 months of study treatment, bone marrow aspirates are required within 7 days prior to study drug administration on Day 1 of every 3 months (i.e., Day 1 of Cycles 10, 13, 16, etc.) for determination of response, at the time of relapse or progressive disease, and at the end of treatment. For patients in follow-up who discontinue study treatment prior to disease progression, bone marrow aspirates and biopsy should be collected every 4 months.

[u] Concomitant therapy consists of any medication (e.g., prescription drugs, vaccines, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening to the study completion or treatment discontinuation visit.

[v] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[w] Two priming doses of 1 mg/kg of Hu5F9-G4 will be administered to patients by continuous IV infusion on Days 1 and 4 of Cycle 1, followed by loading doses of 15 mg/kg on Day 8 and 30 mg/kg on Day 11. Starting on Day 15 of Cycle 1, Hu5F9-G4 maintenance will be given at a dose of 30 mg/kg QW of each 28-day cycle.

[x] Atezolizumab will be administered to patients by IV infusion at a fixed dose of 840 mg, starting on Day 22 of Cycle 1. In subsequent cycles, 840 mg of atezolizumab will be given Q2W on Days 8 and 22 of each 28-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. *For the first two doses of atezolizumab following Hu5F9-G4, at least 60 minutes should be allowed for observation after Hu5F-G4 administration and 60 minutes for observation after atezolizumab administration. If no infusion-associated adverse events are observed during the initial two combination treatment sessions, a 30-minute observation period between Hu5F9-G4 and atezolizumab infusion and a 30-minute observation period after atezolizumab infusion could be considered for subsequent administrations.*

Appendix 1
Schedule of Activities (cont.)

[y] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint(s)	Sample Type
Cycle 1, Day 1	Prior to the first infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
Cycle 1, Day 8	Prior to the first infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
Cycle 1, Day 11	Prior to the first infusion	• Hu5F9-G4 PK (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
Cycle 1, Day 22	Prior to the first infusion of Hu5F9-G4 and atezolizumab	• Atezolizumab PK (serum) • Hu5F9-G4 PK (serum) • Atezolizumab ADA (serum)
	30 (±10) minutes after the atezolizumab infusion	• Atezolizumab PK (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
Cycle 2, Day 1	Prior to the first infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)

ADA = anti-drug antibody; PK = pharmacokinetic.

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

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples (cont.)

Visit	Timepoint(s)	Sample Type
Cycle 2, Day 8	Prior to the first infusion	• Atezolizumab PK (serum) • Hu5F9-G4 PK (serum) • Atezolizumab ADA (serum)
Cycle 2, Day 22	Prior to the first infusion	• Atezolizumab (PK serum) • Atezolizumab ADA (serum)
Cycle 3, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
	1 hour (±15 minutes) after the end of the infusion of Hu5F9-G4	• Hu5F9-G4 PK (serum)
Cycle 3, Day 22	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Cycle 4, Day 22	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Cycle 5, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
Cycle 7, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum)
Cycle 8, Day 22	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; PK = pharmacokinetic.

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

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples (cont.)

Visit	Timepoint(s)	Sample Type
Cycle 9, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum)
Cycle 11, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
Cycle 12, Day 22	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Cycle 13, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum)
Cycle 15, Day 1	Prior to the first infusion	• Hu5F9-G4 PK (serum) • Hu5F9-G4 ADA (serum)
Cycle 16, Day 22	Prior to the first infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Cycle 17, Day 1, and Day 1 of every 2 cycles thereafter	Prior to the first infusion	• Hu5F9-G4 PK (serum)
Treatment discontinuation visit (≤30 days after final dose)	At visit	• Atezolizumab PK (serum) • Hu5F9-G4 PK (serum) • Atezolizumab ADA (serum) • Hu5F9-G4 ADA (serum)
120±30 days after final dose of atezolizumab	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA=anti-drug antibody; PK=pharmacokinetic.

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

Appendix 3
Schedule of Biomarker Samples

Sample Type	Screening	Treatment				At Time of Relapse, PD, or Suspected PD [a, b]	Study Tx Discon [c]	Unscheduled Visit [c]	Survival Follow-Up [d]
		Cycle 1		Cycle 2	Cycle 4				
	Days −28 to −1	Day 1	Day 22	Day 15	Day 1	NA	NA	NA	
Bone marrow aspirate and biopsy	x		x		x	x	x	x	x
Plasma sample		x	x	x	x	x	x	x	
Whole-blood sample		x	x	x	x	x	x	x	

Discon = discontinuation; NA = not applicable; PD = progressive disease; Tx = treatment.

[a] Patients will undergo bone marrow biopsy sample collection, whenever possible, at the time of first evidence of disease progression. Biopsies should be performed within 14 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

[b] If bone marrow aspirate and/or biopsy are collected to confirm suspected PD, the bone marrow samples and the appropriate blood samples should be submitted for biomarker testing.

[c] If the visit at which a response assessment shows relapse or PD resulting in patient discontinuation is used as the treatment discontinuation visit, then an additional sample for study treatment discontinuation does not need to be obtained.

[d] For patients in follow-up who discontinue study treatment prior to disease progression, bone marrow aspirates and biopsy should be collected every 4 months. All bone marrow examinations should be assessed locally (see Section 4.5.7).

Appendix 4
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 5
Response Evaluation Criteria

Category	Definition	Comment
Response		
CR_{MRD-}	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR or CR with negativity by MFC	
CR	Bone marrow blasts $< 5\%$, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, ANC $\geq 1.0 \times 10^9$/L (1000/μL), and platelet count $\geq 100 \times 10^9$/L (100,000/μL)	MRD [a] or unknown
CR_i	All CR criteria except for residual neutropenia ($< 1.0 \times 10^9$/L [1000/μL]) or thrombocytopenia ($< 100 \times 10^9$/L [100,000/μL])	
MLFS	Bone marrow blasts $< 5\%$, absence of blasts with Auer rods, absence of extramedullary disease, and no hematologic recovery required	Marrow should not merely be "aplastic;" at least 200 cells should be enumerated or cellularity should be at least 10%.
Partial remission	All hematologic criteria for CR, decrease of bone marrow blast percentage to 5% to 25%, and decrease of pretreatment bone marrow blast percentage by at least 50%	
Treatment failure		
Primary refractory disease	No CR or CR_i after six courses of investigational treatment, excluding patients who die as a result of aplasia or death because of indeterminate cause	

CR = complete remission; CRi = complete remission with incomplete hematologic recovery; CR_{MRD-} = complete remission without minimal residual disease; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PD = progressive disease; RT-qPCR = real-time quantitative polymerase chain reaction.

[a] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease.

Appendix 5
Response Evaluation Criteria (cont.)

Category	Definition	Comment
Treatment failure (cont.)		
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic, with aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy or <7 days following its completion, or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS, and criteria for PD not met	Period of stable disease that should last for at least 3 months
	Evidence of an increase in percentage of bone marrow blasts and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15%-point increase is required in cases with <30% blasts at baseline, or persistent marrow blast percentage of >70% over at least 3 months, without at least a 100% improvement in ANC to an absolute level (>0.5×10^9/L [500/μL], and/or platelet count to >50×10^9/L [50 000/μL] non-transfused), or • >50% increase in peripheral blasts (WBC × % blasts) to >25×10^9/L (>25 000/μL) (in the absence of differentiation syndrome) [a] or	

CR = complete remission; CRi = complete remission with incomplete hematologic recovery; CR_{MRD-} = complete remission without minimal residual disease; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PD = progressive disease; RT-qPCR = real-time quantitative polymerase chain reaction.

[a] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease.

Appendix 5
Response Evaluation Criteria (cont.)

Category	Definition	Comment
Response criteria for clinical trials only (cont.)		
Progressive disease [a]	New extramedullary disease	
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥ 5%, reappearance of blasts in the blood, or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, recurrence of MRD, as assessed using RT-qPCR or by MFC	

ANC = absolute neutrophil count; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; CR_{MRD} = complete remission without minimal residual disease; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PD = progressive disease; RT-qPCR = real-time quantitative polymerase chain reaction.

[a] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease.

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Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty about autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study. The dose of Hu5F9-G4 may be decreased to 20 mg/kg after consultation with the Medical Monitor.

In general, Hu5F9-G4 dose reductions to 20 mg/kg may be considered for Hu5F9-G4–related toxicities that are Grade 3 or 4; however, the following are generally not reasons for dose reduction:

- Grade 3 anemia: Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling or limiting self-care activities of daily life, may result in dose reduction
- Grade 3 indirect or unconjugated hyperbilirubinemia that resolves to Grade ≤2 with supportive care within 7 days and is not associated with other clinically significant sequelae
- Grade 3 elevation in ALT, AST, or ALP that resolves to Grade ≤2 with supportive care within 1 week and is not associated with other clinically significant sequelae
- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgias, fever, headache, pain during the infusion, or skin toxicity that resolves to Grade ≤2 within ≤72 hours after medical management (e.g., supportive care, including immunosuppressant treatment) has been initiated
- Grade 3 fatigue that resolves to Grade ≤2 within 2 weeks of Day 1 of the next cycle of study treatment
- Grade 3 Hu5F9-G4–related infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia, etc.) that resolve to Grade ≤2 or baseline value within 7 days
- Grade 3 or 4 lymphopenia or leukopenia
- Any Grade 3 autoimmune toxicity that clinically resolves to Grade ≤2 within 7 days of initiating therapy
- Grade 3 diarrhea or skin toxicity that resolves to Grade 1 or better in <7 days after medical management (e.g., immunosuppressant treatment) has been initiated
- Other single laboratory values out of normal range that have no clinical correlate and resolve to Grade ≤2 or to baseline within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Patients who are deemed to require further dose reductions < 20 mg/kg of Hu5F9-G4 should be discontinued from study treatment with Hu5F9-G4.

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 ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the 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.

Hu5F9-G4 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see the Dose Modifications section). If a patient misses three or more consecutive doses during the combination treatment period, the investigator and Medical Monitor will decide whether the patient should discontinue Hu5F9-G4 permanently. If Hu5F9-G4 is withheld for > 28 days because of toxicity, the patient should be discontinued from Hu5F9-G4. However, if the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement, Hu5F9-G4 can be resumed after being withheld for > 28 days. If the time interval between Hu5F9-G4 doses is >4 weeks on account of missed doses, a repriming period is required prior to restarting weekly doses. If repriming is necessary, atezolizumab should be held during the repriming week and restarted when the 30-mg/kg weekly dosing of Hu5F9-G4 begins.

If atezolizumab is discontinued, Hu5F9-G4 should also be discontinued. If Hu5F9-G4 is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

MANAGEMENT GUIDELINES

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 9 for atezolizumab-related adverse events and in the Atezolizumab Investigator's Brochure. This section integrates management guidelines for those adverse events when both atezolizumab and Hu5F9-G4 have developed guidance. This section also includes generic guidance for management of Hu5F9-G4

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

when atezolizumab-associated adverse events occur. This section includes management guidelines for Hu5F9-G4–associated adverse events. For cases in which management guidelines are not covered in Appendix 9, the Hu5F9-G4 Investigator's Brochure, or the protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

INFUSION-RELATED REACTIONS AND ANAPHYLAXIS

Management guidelines for patients who experience infusion-related reactions or anaphylaxis are presented in Table 1.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events Associated with Hu5F9-G4

Event	Action to Be Taken
IRRs and anaphylaxis	
IRR, Grade 1	• Follow guidelines for atezolizumab in Appendix 9. • For anaphylaxis precautions, see Appendix 7.
IRR, Grade 2	• Follow guidelines for atezolizumab in Appendix 9. • For anaphylaxis precautions, see Appendix 7. • For Hu5F9-G4: – Stop the Hu5F9-G4 infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV or equivalent and/or 500 to 750 mg oral paracetamol/acetaminophen. – Remain at bedside and monitor patient until resolution of symptoms. – Corticosteroid therapy may also be administered at the discretion of the investigator. – If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate when symptoms resolve. – If symptoms recur, then stop infusion and disconnect the patient from the infusion apparatus; no further Hu5F9-G4 will be administered at that visit. The amount of study drug infused must be recorded on the electronic Case Report Form. – Patients who experience an infusion reaction of Grade 2 during the 4-hour post-infusion observation period that does not resolve during that time should be observed for 24 hours or until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.

IRR = infusion-related reaction.

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Table 1 Guidelines for Management of Patients Who Experience Adverse Events Associated with Hu5F9-G4 (cont.)

Event	Action to Be Taken
IRRs and anaphylaxis (cont.)	
IRR, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 9. • For anaphylaxis precautions, see Appendix 7. • For Hu5F9-G4: – Stop infusion and permanently discontinue Hu5F9-G4. – Begin an IV infusion of normal saline, and treat the patient as follows: administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or equivalent, as needed. – Administer aggressive symptomatic treatment. – All patients will be observed for an additional 24 hours or longer until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 9. • Continue Hu5F9-G4.
Grade 3	• Follow guidelines for atezolizumab in Appendix 9. • Continue Hu5F9-G4.
Grade 4	• Follow guidelines for atezolizumab in Appendix 9. • Hu5F9-G4 may be continued at the discretion of the investigator per medical judgment.

IRR=infusion-related reaction.

Hu5F9-G4–ASSOCIATED ANEMIA

Anemia, Blood Crosmatching, and Packed RBC Transfusion Procedures

Hu5F9-G4 binds to RBCs and leads to erythrophagocytosis. This, coupled with anemia from other cause in patients with cancers, means that care has to be taken with RBC crossmatching and packed RBC transfusions. There is a possibility that treatment with Hu5F9-G4 may obscure assessment of RBC phenotyping, although this has not been observed in patients to date.

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

At baseline, prior to initiation of Hu5F9-G4 therapy, blood cell ABO phenotyping for minor antigens, type, and screen (ABO blood type and Rhesus [Rh] factor), and direct antibody testing (DAT) will be performed to facilitate, together with the prior phenotype, allocation of properly crossmatched blood in the event a blood transfusion is warranted.

For patients after exposure to Hu5F9-G4, ABO, Rh, and DAT may be pan-reactive because of Hu5F9-G4 binding to RBCs. Therefore, if a non-urgent transfusion is ordered by the investigator, perform the following procedures:

- Front type: EGA-treated cells ($\times$2 maximum) and warm wash $\times$4 (minimum) with 0.9% saline
- Back type: Perform reverse anti-human globulin for both A and B.
- If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.
- Antibody screen

If a pan-agglutinin/warm autoantibody is present in low-ionic-strength solution, repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all specified blood groups proves impractical (e.g., for MNS), local sites will decide on the best-matched donor units to be used. Cytomegalovirus (CMV) matching (i.e., CMV-seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If the crossmatch is incompatible, the RBC units that are Coombs crossmatched incompatible will be selected (e.g., phenotype matched or least incompatible) for issue at the discretion of the sites' transfusion Service Medial Director or equivalent person, where available.

Hu5F9-G4 Impact on Red Blood Cell Transfusion Procedures

Hu5F9-G4 binds to red cells and leads to erythrophagocytosis. This, coupled with anemia from other causes in patients with cancers, means that care has to be taken with RBC crossmatching and packed RBC transfusions. There is a possibility that treatment with Hu5F9-G4 may obscure assessment of RBC phenotyping, although this has not been observed in patients treated to date.

Appendix 8
Overall Guidelines for Management of Patients Who Experience Adverse Events (cont.)

During the screening period prior to initiation of Hu5F9-G4 therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and DAT will be performed for each patient. This, together with using the prior phenotype, will facilitate allocation of properly crossmatched blood in the event a blood transfusion is warranted.

For patients after exposure to Hu5F9-G4:

- ABO, Rh, and DAT may be pan-reactive owing to Hu5F9-G4 binding to red cells. Therefore, if a non-urgent transfusion is ordered by the investigator, perform the following procedures:
  - Front type: EGA-treated cells (approximately 2 maximum) and warm wash (approximately 4 minimum) with 0.9% saline.
  - Back type: Perform reverse anti-human globulin for both A and B.
  - If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.
- Antibody screen:

  If a pan-agglutinin or warm autoantibody is present in low ionic strength solution, repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rh-negative units if the phenotyped units are not available.

Blood plasma therapy will be blood type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high-titer anti-A or anti-B.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated 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.

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 also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic 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]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
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 test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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-mediated 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-mediated 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 three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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-mediated 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.

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.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 patient 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 patient 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-mediated hyperthyroidism. [c]

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact 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 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 the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated 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-mediated 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • 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. • 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [f] • 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. [e] • 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. [f] • 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. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq 38°C$ 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] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] 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.

[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • 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. • 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]

[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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated 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-mediated 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.

[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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated 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.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

RENAL EVENTS

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

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

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOSITIS

Immune-mediated 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 13.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for Immune-Related Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact 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]

[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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact 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.
Immune-mediated 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-mediated 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.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.

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 ≥ 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 $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 and/or an immunosuppressive agent. • 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.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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