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NCT Number:	NCT03154827
Sponsor Study Number:	BL-8040.AML.202
Official Study Title:	Phase Ib/II, Multicenter, Single Arm, Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia - The BATTLE Study
Document Version and Date:	Clinical Study Protocol, version 4.0, 27 January 2019

Investigational Product BL-8040 & Atezolizumab	A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia - The BATTLE Study	**Protocol No.** BL-8040.AML.202
Phase: Ib/II		Version 4.0 27 January 2019

CLINICAL STUDY PROTOCOL

A PHASE IB/II, MULTICENTER, SINGLE ARM, OPEN-LABEL STUDY, TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF THE BL-8040 AND ATEZOLIZUMAB COMBINATION FOR MAINTENANCE TREATMENT IN SUBJECTS WITH ACUTE MYELOID LEUKEMIA - THE BATTLE STUDY

Sponsors: BioLineRx, Ltd.
[redacted]

IND No. [redacted]

Investigational Medicinal Products:
1. BL-8040 (previously BKT-140)
2. Atezolizumab

Study coordinating Principal Investigator(s): [redacted]

Protocol Number: BL-8040.AML.202

Study Phase: Ib/II

Sponsor Contact: [redacted]

Study Safety Officer: [redacted]

Protocol Version and Date: Version 4.0, 27 January 2019

Confidentiality Statement

This protocol is a confidential communication document of BioLineRx, Ltd. The recipient of this document agrees not to disclose the information contained herein to others without prior written authorization of BioLineRx, Ltd. except that this document may be disclosed to appropriate Institutional Review Boards/Independent Ethics Committees or duly authorized representatives of Regulatory authorities, under the condition that they maintain confidentiality.

Protocol Signature Page

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Protocol Identification	BL-8040.AML.202
Study Phase	Ib/II
Sponsor	BioLineRx Ltd., ISRAEL

Sponsor Representatives

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and applicable local regulations.

[redacted]

VP Clinical and Medical Affairs

4-FEB-2019

Date

[redacted]

VP R&D

4-Feb-2019

Date

Investigational Product BL-8040 & Atezolizumab	A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia - The BATTLE Study	**Protocol No.** BL-8040.AML.202
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Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, CRF and any protocol-related documents (subject to any amendments agreed to in writing between the Sponsor and Principal Investigator). I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of BioLineRx Ltd. I understand that the study may be terminated, or enrollment suspended at any time by sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study subjects.

Name	Investigator Signature	Date

Center's Name	City, Country

Protocol Version History Page

Version	Main Changes
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Version	Main Changes
[redacted]	[redacted]
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Protocol Synopsis

Study Title	A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia– The BATTLE Study
Protocol No.	BL-8040.AML.202
Clinical Sites	USA-5 sites, Israel-2 sites, EU-20 sites Optional: Other countries and sites may be added
Study Phase	Ib/II
Planned Sample Size	A total of up to 60 subjects will be enrolled in two study periods: • Initial Risk-Benefit Period of 12 subjects • Expansion Period of up to 48 additional subjects
Therapeutic Indication	Maintenance therapy in Acute Myeloid Leukemia (AML) subjects ≥ in first Complete Remission (CR1), who are not planned for stem cell transplantation.
Study Objectives	**Primary Study Objective - Safety and Tolerability:** To demonstrate that the proposed combination is safe and tolerated. **Secondary Study Objectives - Efficacy:** • To assess the relapse free survival (RFS) time in subjects treated with the combination of BL-8040 and Atezolizumab for maintenance. • To demonstrate that the combination of BL-8040 and Atezolizumab reduces the Minimal Residual Disease (MRD) as compared to baseline. • To assess the Overall Survival (OS) time in subjects treated with the combination of BL-8040 and Atezolizumab for maintenance. • To assess the Event Free Survival (EFS) time in subjects treated with the combination of BL-8040 and Atezolizumab for maintenance.
Study Design	This is a single arm, open label, Phase Ib/II study in which eligible subjects will receive maintenance treatment consisting of intravenous (IV) infusion of 1200 mg Atezolizumab on Day 2 of each 21-day cycle and subcutaneous (SC) injections of BL-8040 (1.25mg/kg) on Days 1, 2 and 3 of each 21-day cycle. Cycles will be repeated for up to 2 years (a maximum of 34 treatment cycles), until early discontinuation for any reason or until disease relapse, whichever comes first. Patients in CR1 will be recruited after induction, with 1-4 cycles of cytarabine-based consolidation therapy, unless they have been deemed intolerant or,

refused to receive consolidation therapy or they receive treatment with at least 3 cycles of Hypomethylating agents (HMA).

The study will recruit an initial Risk-Benefit period staggered cohort of up to 12 subjects in order to establish the safety, tolerability and efficacy of the combination treatment before opening enrollment to the full study population. Safety data will be reviewed by an independent Data Monitoring Committee (DMC).

Hematology (CBC) assessment will be performed before each dose of BL-8040. BL-8040 injections will be skipped in case of a significant increase in white blood cells (WBCs) (WBC ≥ 60,000/μL) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis. When WBC is reduced below 60,000/μL Treatment can be resumed. Missed doses can be skipped until the WBC count has decreased to < 60,000/μL up to 2 Cycles. Missed doses will not be made up if >72 h have passed. If the delay is beyond the 2 Cycles, the Medical Monitor should be consulted in order to assess the continuation of the study for the specific subject. The pre dosing monitoring of WBC should be continued until WBC is below 40,000 /μL.

Dose Limiting Toxicities and Ongoing Safety Assessment

Adverse events (AEs) will be reported from the time of informed consent until 30 days after the last dose of study drug. The period considered for dose-limiting toxicity (DLT) assessment will be limited to the first cycle of therapy defined as the time from the first dose of BL-8040 up to and including the day when the first cycle of combination therapy ends (usually Day 21). Beyond the DLT assessment period, AE data will be collected on an ongoing basis and recorded within the CRF. However, these events will not be considered for DLT evaluation.

Dose-limiting toxicity (DLT) is defined as a clinically significant adverse event (AE) or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the first treatment cycle that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematological NCI common terminology criteria that are CTCAE grade 3 or 4
- Change from baseline to Grade 4 neutropenia or thrombocytopenia lasting for >4 weeks in the absence of persistent Leukemia
- Symptomatic leukostasis

To be considered a DLT the toxicity must be possibly, probably or definitely related to either of the study drugs or the combination.
An AE must be clinically significant to define DLT, e.g., nausea and vomiting, alopecia, study drug-related fever or electrolyte abnormalities that are ≤ Grade 3 will not constitute DLT. For subjects who experience a DLT, the study

continuation should be discussed with the Medical Monitor. Subjects who experience AEs that are not considered DLT or are unrelated to BL-8040 or Atezolizumab may continue study participation at the discretion of the Investigator.
BL-8040 injections may be skipped for any reason per Investigator judgment; however, they must be skipped in the case of a WBC >60,000/µL, measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis.
Increase in WBC is not considered a DLT since it is a direct effect of CXCR4 inhibition and reflects the drug's mechanism of action.
In case of elevated WBC > 60,000/µL, daily WBC assessment should be done. When WBC is reduced to or below 60,000/µL treatment can be resumed. The Pre-dosing monitoring of WBC should be continued until WBC is below 40,000/µL and further analysis should be done based on the Investigator's judgment.

The study will consist of two periods:

- Initial Risk-Benefit Period which will enroll a total of 12 subjects. The decision whether to continue to the extension phase will be made based on a risk-benefit analysis and data review by the DMC together with the Sponsor.
- Expansion Period of additional up to 48 subjects.

Safety review of the accumulated data will be performed by an independent DMC after the first 6 subjects have completed the first cycle of combination therapy and again after 6 additional subjects have completed the first cycle of combination therapy. Guidelines to be used by the DMC for the review of the proposed combination toxicity are presented below:

- If ≤1 out of 6 subjects experience a DLT during the first cycle of treatment, enrollment should be expended to include 6 additional subjects.
- If ≥ 2 out of 6 subjects experiences a DLT, the DMC will assess the risk/benefit profile of the combination treatment and recommend one or more of the following: 1) Recruitment should continue to include additional 6 subjects, 2) the protocol should be modified, 3) the treatment schedule should be modified or 4) the study should be discontinued.
- If ≤ 2 out of 12 subjects experience a DLT the DMC will recommend the recruitment of additional 3 subjects for the completion of the pre-planned Initial Risk-Benefit Period population size of 12 subjects. .
- If >2 out of 12 subjects experience a DLT, the DMC will recommend one or more of the following: 1) Recruitment should be continued to include 3 additional subjects for the completion of the pre-planned

	Initial Risk-Benefit Period population size of 12 subjects, 2) the protocol should be modified, 3) the treatment schedule should be modified or 4) the study should be discontinued. Following the completion of the Initial Risk-Benefit Period which is planned to enroll a total of 12 subjects, an integrative analysis of risk-benefit of the proposed combination will be performed. Then, the DMC, in collaboration with the Sponsor, based on an assessment of the integrated database will decide whether to continue to the Expansion Period and to enroll 48 additional subjects or to discontinue the study. The number of subjects planned for DLT assessment will be up to 12 subjects, recruited in a staggered manner, not exceeding the potential for observing that the proposed combination therapy would be considered unacceptably toxic according to the criteria above. In order to be evaluable for the DLT assessment period, a subject must complete the first cycle of treatment. If a subject is discontinued before completion of the first cycle (unless due to a DLT), he/she will be replaced by an additional subject ensuring that the pre-planned size of 12 subjects for DLT assessment is preserved. The subjects that are discontinued early will be included in all the other relevant analyses according to the population described in the statistical analysis section. Clinical sites are required to contact the Sponsor within 24 hours in case subjects present suspected DLTs during the assessment period. After completion of the DLT assessment period, further DMC assessments will be continued according to the DMC charter to be finalized before study recruitment.
Study Procedures, Periods and Duration	For a detailed description of the study procedures see schedule of assessments (Appendix A). Study planned periods are displayed below: **Study Period** / **Duration** Screening period — Up to 28 days Treatment Period — 21-day cycles for up to 24 months for a maximum of 34 cycles Post-Treatment Safety Follow-Up — At 30 days from last study drug cycle. May be extended for up to 90 days Long-Term Survival Period — Every 3 months following Treatment Period during an additional period of the later of 5 years or till End of Study for AML status and survival **Screening Period**: The purpose and procedures of the study will be fully explained to the participants. Those wishing to be enrolled in the study will sign a written informed consent prior to initiating any evaluations or study-related procedures. Following the signing of informed consent, subjects will undergo screening period procedures during the period of up to 28 days and will be evaluated for study eligibility.

	Treatment Period: Eligible subjects will receive maintenance treatment consisting of intravenous (IV) infusion of Atezolizumab on Day 2 of each 21-day cycle and subcutaneous (SC) injections of BL-8040 on Days 1, 2 and 3 of each 21-day cycle. Cycles will be repeated for up to 2 years (a maximum of 34 treatment cycles), until early discontinuation for any reason or until disease relapse, whichever comes first. **Post-Treatment Safety Follow-Up**: Assessment will be performed at 30 days after the last dose of study drug. The period might be extended for up to 90 days after the last dose of study drug for any SAEs considered to have a reasonable possibility of being related to BL-8040 and/or Atezolizumab. **Long-Term Survival Follow-Up:** Subjects will be contacted by phone every 3 months after termination/early termination of the Treatment Period in order to follow survival and AML status. Follow up will be done for an additional period of 5 years or until End of Study, whichever comes later. **Study Duration**: The study will end no longer than 84 months after the last enrolled subject was administered with the 1st study drug, if the preliminary phase and extension will be enrolled. Assuming an enrolment period of 18 months, the study is planned to be ended no longer than 102 months (8.5 years) after the 1st study drug administration of the first enrolled subject (hereafter, referred to as "End of Study"). **Individual Subject Study Participation**: The study duration for an individual subject depends on RFS duration. Treatment cycles will continue until the earlier of relapse, death, intolerable toxicity or any other reason for early discontinuation for up to 24 months for a maximum of 34 treatment cycles. Following Treatment Period, subjects who are RFS will continue to be followed-up every 3 months during the Long-Term Survival Period until End of Study.

Inclusion Criteria	1. Adult men and women aged ≥ 18 years. 2. Confirmed diagnosis of AML (according to WHO criteria. See Appendix C) 3. Subjects with newly diagnosed AML who have achieved Complete Remission (CR or Cri), after a. Up to two cycles of cytarabine based induction chemotherapy. b. A minimum of 3 cycles of hypomethylating agent (HMA) such as: azacytidine, decitabine, etc. 4. Subjects with intermediate or adverse risk factors according to the ENL guidelines 2017a.

[a] Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Döhner H. et al, Blood, 26 January 2017 X Volume 129, Number 4-Appendix F

	5. CR (or CRi) must be confirmed by bone marrow aspirate up to 28 days prior to enrollment. 6. Subjects who have received 1-4 cycles of consolidation therapy unless they have been deemed intolerant, or have refused consolidation therapy, or subjects that received at least 3 cycles of HMA. 7. Subjects who prior to screening are MRD positive according to local laboratory or with an unknown MRD status; are to be confirmed or tested, respectively, for MRD by central laboratory prior to enrollment. 8. Subjects who were diagnosed with AML within 18 months prior to study enrollment. 9. Subjects should have received the last dose /of induction, consolidation or HMA, whichever comes later, within 6 months prior to study enrollment 10. Subjects who, at the time of enrollment, are not planned for allogeneic stem cell transplantation. 11. Female subjects must be post-menopausal or of non-childbearing potential defined as absence of menses for > 1 year or those who have had a bilateral tubal ligation or hysterectomy. 12. Male subjects with partners of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study therapy through at least 5 months after the last dose of study therapy. Examples of adequate methods are: for males- condom with or without spermicide, sexual abstinence or surgical sterility (vasectomy) or for female partners with childbearing potential- oral, transdermal patch, implanted contraceptives, intrauterine device, diaphragm. 13. Subject is able and willing to comply with the requirements of the protocol. 14. Subject is able to voluntarily provide written informed consent prior to the initiation of any screening or study-related procedures

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Exclusion criteria	1. Subjects diagnosed with acute promyelocytic leukemia. 2. Subjects with extramedullary AML, including CNS involvement. 3. Subjects who have achieved CR or CRi following treatment for relapsed or refractory AML after 2 inductions. 4. Subjects in CR1 following allogeneic stem cell transplantation. 5. Subjects who are candidates for allogeneic stem cell transplantation and have a suitable donor. 6. Life expectancy of ≤ 6 months. 7. Clinically significant abnormal laboratory safety test values including, but not limited to: o Total bilirubin > 2 times upper limit of normal (x ULN) o Aspartate Aminotransferase (AST/SGOT) or Alanine Aminotransferase (ALT/SGPT) > 2 x ULN o Creatinine > 1.5 x ULN or GFR < 30 mL/min. 8. Low Performance Status (ECOG > 2; Appendix D) 9. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor alpha [anti–TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions: o Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contact allergy) are eligible for the study after Medical Monitor approval has been obtained. o Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study. o Requirement for use of denosumab during the study: Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study. 10. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five

	half-lives of the drug (whichever is longer) prior to initiation of study treatment. 11. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with Atezolizumab or within 5 months after the last dose of Atezolizumab 12. Prior treatment with immune checkpoint blockade therapies (anti−CTLA-4, anti−PD-1, or anti−PD-L1) or immune agonists (anti-CD137, anti-CD40, anti-OX40). 13. Known allergy or hypersensitivity to any of the test compounds, materials or contraindication to test product, including: o History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies or fusion proteins o Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the Atezolizumab formulation. 14. Use of investigational device or drug within 2 weeks or five half-lives, whichever is longer, prior to the enrolment date. 15. Past or current history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune myocarditis, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions: o Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study. o Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study. o Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: ▪ Rash must cover <10% of body surface area ▪ The disease is well controlled at baseline and requires only low-potency topical corticosteroids ▪ No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids,

	biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months. 16. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 17. Serious infection requiring oral or IV antibiotics, antifungals, antivirals, and/or hospitalization within 14 days prior to Cycle 1, Day 1 ▪ Patients who receive prophylactic oral antibiotics, antifungals, and antivirals as a result of prolonged neutropenia in the absence of documented infection are eligible. ▪ Patients being treated for non-serious, infectious complications (e.g., oral candidiasis or uncomplicated urinary tract infection) with oral and/or topical antimicrobials may be eligible for study treatment (antimicrobials must be completed, prior to Cycle 1, Day 1 and all cases must be discussed with and approved by the Medical Monitor). 18. Subjects with history of organ or stem cell transplantation. 19. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease and inherited liver disease. 20. Active tuberculosis. 21. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 12 months prior to initiation of study treatment, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment. 22. Grade $\geq$ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment. 23. Positive HIV test at screening or at any time prior to screening. 24. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study. 25. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

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	26. Subjects with concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness which could place him/her at unacceptable risk, including, but not limited to: o History of malignancy other than AML 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 o Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. o Unable to comply with study requirements in the opinion of the Investigator.
Investigational Product Route and Dosage Form	**<u>BL-8040 (formerly named BKT140)</u>** A highly selective CXC chemokine 4 receptor (CXCR4) antagonist developed by BioLineRx, Ltd. as a novel therapy for treatment of cancer. BL-8040 is a white to off-white powder comprised of synthetic polypeptide, which is freely soluble in water. Subjects will receive once daily SC injections of 1.25 mg/kg of BL-8040 after CBC assessment on Days 1, 2 and 3 of each 21-day cycle. On Day 2, BL-8040 will be administered 1 h (± 30 min) after the end of the Atezolizumab infusion. The BL-8040 injection site will be rotated daily, to minimize the severity of any local injection site reactions. When the reconstitution volume is > 2 mL, the injection should be split in order to have less than 2 ml per injection and administered into more than one site (e.g. hand and leg). At the discretion of the Investigator, lower volumes may be split and injected into more than one site. **<u>Atezolizumab</u>** The Atezolizumab drug product will be supplied by the Sponsor in a single-use, 20 mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free, clear liquid solution intended for IV administration. For information on the formulation and handling of Atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure. Subjects will receive Atezolizumab 1200 mg IV on Day 2 of every cycle. The first infusion of Atezolizumab should be administered over 60 mins. If well tolerated, subsequent infusions may be performed over 30 mins.

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Concomitant Medications	All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medications received within 30 days prior to the screening visit and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of study treatment will be recorded when related to SAEs. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included in the CRF. Transient hypotension, due to vaso-vagal episodes, was witnessed in several cases following the first treatment with BL-8040. Therefore, caution should be taken with the use of negative chronotropic drugs such as beta blockers. When appropriate, negative chronotropes should be replaced by non-chronotropic alternatives. Pre-medication and allowed medication for BL-8040 adverse event management: • *Premedication* prior to BL-8040 injection with antihistamines (e.g. diphenhydramine, promethazine, etc.) in order to minimize the occurrence of BL-8040 related systemic reactions is highly recommended. • Systemic steroids are allowed for the treatment of systemic reaction but not as regular pre-medication of these reactions. • Clinically appropriate measures in case of BL-8040-related local injection site reactions e.g., local corticosteroids, systemic and local painkillers, antihistamines, local treatments etc. are allowed. **Permitted Concomitant Medications** • Antiemetic drugs (e.g., ondansetron) as required clinically based on local guidelines for subjects experiencing nausea. • Prophylactic antibiotics (e.g., quinolone or cephalosporin), anti-fungals (e.g., voriconazole) and antivirals (e.g., valacyclovir) when appropriate. • Blood products that are commonly required in oncology subjects. • Low-dose steroids are allowed as pre-medication for blood transfusion or with IV anti-fungals. • Vitamins, nutritional supplements, herbal supplements and over the counter medications are permitted per PI's judgement.

- Vitamin D therapy.
- Polyphenols in green tea/supplements

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the screening period and treatment phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy or other therapy not specified in this protocol.
- Investigational agents other than BL-8040 and Atezolizumab.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial and 5 months after the last dose of Atezolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed viruses and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Lodonal
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or for systemic and local reactions secondary to BL-8040 and/or Atezolizumab treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. *Note: Inhaled steroids are allowed for management of asthma, and dermatological formulations are allowed to reduce the intensity of injection site reactions.*
- Medications or vaccinations specifically prohibited in the Exclusion Criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's trial therapy requires mutual agreement of the Investigator, the Sponsor, and the subject.

Subjects who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

No live attenuated vaccines can be given up to 5 months post last dose.

Investigational Product BL-8040 & Atezolizumab	A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia - The BATTLE Study	**Protocol No.** BL-8040.AML.202
Phase: Ib/II		Version 4.0 27 January 2019

Study Endpoints	**Primary Safety and Tolerability Endpoints and Outcome Measures:** • Dose Limiting Toxicity (DLT). • Adverse Events and serious adverse events. • 12-Lead ECG. • Vital Signs. • Safety laboratory tests. • Early discontinuations; reasons and time to event. **Secondary Efficacy Endpoints** • Time from CR to the occurrence of earlier relapse or death from any cause (RFS). • Change from baseline to Cycles 3, 9, 18 and 34 in MRD status measured using quantitative, multi-color, flow cytometry. • Time from 1st study drug administration to death from any cause (OS). • Event Free Survival (EFS) measured as the earlier from 1st study drug administration to the date of primary refractory disease, or relapse from CR, or death from any cause from 1st study drug administration. **Pharmacokinetics** Characterize the PK profile of BL-8040 and Atezolizumab. **Exploratory Outcome Measures** • Biomarkers that may serve as surrogates or predictors of clinical efficacy (PD-L1 expression, CXCR4 expression, and presence of immune cells). • Immune response to BL-8040 and Atezolizumab. • Presence of ADAs during the study relative to the presence of ADAs at baseline. • Pharmacodynamic endpoints. • Measurement of mast cell activation • Molecular tests may be assessed following emerging public domain literature and other clinical trials with BL-8040.
Statistical Analysis	**Sample Size Justification:** This is a single arm, open-label, phase Ib/II study designed to evaluate the safety, tolerability and to initially assess the effectiveness of the proposed combination therapy. Therefore, neither power assessment, nor formal hypothesis testing are currently planned for study outcome measures. The study will consist of two periods: • Initial Risk-Benefit Period which will enroll up to a total of 12 subjects. The decision whether to continue to the extension phase will

	be made based on a risk-benefit analysis and data review by the DMC together with the Sponsor. Within this study period, the 12 initially recruited patients are considered appropriate for the evaluation of the DLT rate of the proposed combination. • Expansion Period of additional up to 48 subjects. The total planned sample size of up to 60 subjects is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of the proposed combination maintenance therapy in subjects with acute myeloid leukemia. Comprehensive interim reports of accumulated safety, tolerability and preliminary available efficacy data will be presented to the independent Data Monitoring Committee (DMC) periodically in line with the DMC charter. All measured variables and derived parameters will be listed individually and if appropriate, presented in summary tables by potential study population subgroups and overall, providing sample size, absolute and relative frequency for categorical variables, or sample size, arithmetic mean, standard deviation, median, minimum and maximum for continuous variables. Confidence intervals will be presented for the efficacy endpoints for exploratory purposes only. **Statistical Analysis Plan (SAP):** A detailed Statistical Analysis Plan (SAP) will be developed following the recruitment of the 40th subject.

Investigational Product BL-8040 & Atezolizumab	A Phase Ib/II, Multicenter, Single Arm, Open-Label Study, To Evaluate the Safety, Tolerability and Efficacy of the BL-8040 and Atezolizumab Combination for Maintenance Treatment in Subjects with Acute Myeloid Leukemia - The BATTLE Study	**Protocol No.** BL-8040.AML.202
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GLOSSARY

Subject and patient will be used interchangeably throughout this document.

Abbreviation/Term	Definition
λ_z	Elimination rate constant
µL	Microliter
ADA	Anti-drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Transaminase/Serum Glutamic Pyruvic Transaminase
AML	Acute Myeloid Leukemia
aPTT	Activated Partial Thromboplastin Time
Ara-C	Arabinofuranosyl Cytidine / Cytarabine / Cytosine Arabinoside
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
AUC	Area under the curve
BM	Bone Marrow
C_{max}	Maximum plasma concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CR	Complete Remission
CR1	First Complete Remission
CRF	Case Report Form
Cri	Complete Response with Incomplete Hematological Recovery
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	CXC Chemokine Receptor Type 4
DFS	Disease Free Survival
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FACS	Fluorescence-activated cell sorting

Abbreviation/Term	Definition
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
h	Hour
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCT	Hematocrit
HCV	Hepatitis C Virus
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating agent
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG1	Immunoglobulin G1
IMP	Investigational Medicinal Product
INR	International Normalized Ratio (for blood coagulation tests)
IRB/IEC	Institutional Review Board / Independent Ethics Committee
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
L	Liter
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDR	Multi Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MM	Multiple Myeloma
MRD	Minimal Residual Disease

Abbreviation/Term	Definition
NCI	National Cancer Institute
NK	Natural Killer
OS	Overall Survival
PD	Pharmacodynamic
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death-ligand 1
PK	Pharmacokinetic
PT	Prothrombin Time
QA	Quality Assurance
RBC	Red Blood Cell
RFS	Relapse Free Survival
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance, Epidemiology and End Results
SOC	System Organ Class
SOP	Standard Operation Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Elimination Half-Life, Defined as $0.693/\lambda_z$
T_{max}	Time to Reach the Maximum Plasma Concentration
TTR	Time to Relapse
ULN	Upper Limit of Normal
US	United States
USP	United State Pharmacopeia
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Therapeutic Indication

Acute myeloid leukemia (AML) represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate and over proliferation in the stem cell compartment result in accumulation of non-functional cells termed myeloblasts (Stone RM, et al. 2004). The annual age-adjusted incidence of AML in the US is 3.6 cases per 100,000 people (2005 - 2009), with a median age at diagnosis of 66 years. The five-year relative survival in US patients diagnosed over the period 2002-2008 was 23.4% (SEER [Surveillance, Epidemiology and End Results] Cancer Statistics Review 2005-2009).

Standard AML induction therapy consists of 7-day treatment with cytarabine (Ara-C) and 3-day treatment with daunorubicin or idarubicin (7+3 schedule). The goal of induction therapy is to achieve a complete hematological remission (CR), correlating to a reduction of blasts by 3 log-levels, and reflected in a normalized cellularity of the bone marrow with less than 5% blasts and normalization of the peripheral blood count, with neutrophils > $1x10^9$/L and platelets > $100x10^9$/L. Additional defining characteristics of CR are the absence of blasts with Auer rods, absence of extramedullary disease and independence from red cell transfusions. Complete Remission with incomplete haematological recovery (CRi) has the same characteristics with the exception of residual neutropenia (< $1x10^9$/L) or thrombocytopenia (< $100x10^9$/L).

After complete remission (CR) is achieved, consolidation therapy should optimally lead to further reduction of residual leukemic load and reduction of relapse risk. Consolidation therapy is generally performed according to a relapse-risk stratification approach in order to balance therapeutic risks and benefits. Low risk patients receive high-dose Ara-C or high-dose Ara-C plus autologous stem cell transplantation (Byrd JC et al., 2004). Intermediate-risk patients receive high-dose Ara-C or allogeneic stem cell transplantation. High risk patients receive allogeneic stem cell transplantation, preferentially a treatment within a clinical trial or high-dose Ara-C.

Given the available treatment options for AML patients that are not candidates for allogeneic stem cell transplant, there is a clear unmet need for improved therapies to improve patient outcomes.

1.1.1 The Prognostic and Therapeutic Relevance of Minimal Residual Disease

The recent availability of sensitive assays with the ability to detect residual, sub-microscopic leukemia on the basis of leukemia-specific features such as aberrant immune phenotypes and abnormal molecular markers have rekindled the interest in minimal residual disease (MRD). Achieving MRD-negative status according to multiparameter flow cytometry is associated with a highly significant improvement in the outcomes of younger patients with AML receiving Ara-C plus idarubicin-based induction and consolidation regimens (Ravandi F et al., 2016).

Another work found that the long-term outcome of AML patients is strongly influenced by their pre-allogeneic stem cell transplant MRD results as assessed by 10-color multi-parametric FACS (fluorescence-activated cell sorting) analysis on BM aspirates. Three-year relapse estimates were 67% in patients in MRD-positive morphologic remission, 65% in patients with active AML compared to 22% of patients in MRD-negative remission. Three-year OS estimates were 26%, 23% and 73% in these three groups (Araki D et al., 2016). Moreover, the negative impact of pre-transplant MRD is similar for AML in first and second complete remission and associated with adverse outcome (Walter RB et al., 2013).

Elderly patients reached post-consolidation MRD negative status less frequently than younger patients (11 vs 28%, p=0.009) (Buccisano F et al., 2015). However, in elderly patients, MRD negativity resulted in a longer 5-year disease-free survival (DFS) (57 vs 13%, p=0.0197), compared to younger patients (56 vs 31%, p=0.0017). These results underline the importance of MRD negativity for disease outcome in both young and older AML patients.

1.2 Investigational Therapy

1.2.1 BL-8040

BL-8040 is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring. BL-8040 binds and inhibits the CXCR4 chemokine receptor with high affinity (IC_{50} 0.54 - 4.5 nM). It was shown in vitro and in vivo to be a specific antagonist of CXCR4, and to have a slow dissociation rate from the receptor. The chemokine CXCL12 (SDF-1-stromal-derived-factor-1) and its receptor, CXCR4, play a pivotal role in the trafficking of hematopoietic stem cells to the bone marrow (BM). In in-vivo animal studies, as well as in the clinical setting, BL-8040 has demonstrated accelerated mobilization of adult WBCs (neutrophils, monocytes, lymphocytes) and normal stem-cells. In addition to its activity as a mobilizer of WBCs, BL-8040 exhibits a CXCR4-dependent selective cytotoxicity toward malignant cells of hematopoietic origin. BL-8040 significantly and preferentially stimulated apoptotic cell death of cells from AML patients (Beider K et al., 2011).

1.2.1.1 Nonclinical Studies of BL-8040

The nonclinical development of BL-8040 has encompassed a large number of pharmacodynamic (PD), pharmacokinetic (PK), safety pharmacology, and single and repeated dose toxicity studies[a].

BL-8040 exhibits CXCR4-dependent selective cytotoxicity toward malignant cells both in vivo and in vitro and induces apoptotic cell death in cancer cells (Beider K et al., 2011, Beider K et al., 2014, Tavor S et al., 2013). BL-8040 leads to phospharidylserine externalization, decreased mitochondrial membrane potential, caspase activation, subsequent sub-G1 arrest and DNA double-stranded breaks in leukemic and multiple myeloma (MM) cells (Beider K et al., 2011). These effects were shown to be specific; BL-8040 did not affect the viability of human keratinocytes and normal human hematopoietic cells (Beider K et al., 2011). These direct apoptotic effects in addition to the mobilization capacity, distinguishes BL-8040 from other CXCR4 antagonists such as mozobil/plerixafor (Beider K et al., 2011). Furthermore, administration of BL-8040 induces the mobilization of natural killer (NK) cells, T cells and B cells from the bone marrow (BM) and lymph nodes into the periphery. Using a syngeneic cancer model in mice it was demonstrated that BL-8040 may eliminate the immunological barrier and allow the accumulation of immune cells within the tumor microenvironment (unpublished data).

BL-8040 exhibited very high binding to human plasma proteins (99.2%) and high binding to the proteins in rat and dog plasma (94.9-96.9%) in the range of tested concentrations.

The subcutaneous injection (SC) of BL-8040 was tested in GLP toxicology studies in dogs, and rats with the main identified AE's being a transient and local erythema at the injection site and peripheral edema. These reactions were noticed from a few minutes up to approximately 2 hours following the injection. There were no significant changes in terms of histopathology,

[a] The active peptide doses referred to in the "Nonclinical Studies" section are 80.63±1.18% of the indicated dose in the text. The indicated doses were calculated based on total content (including active peptide, peptide impurities, acetic acid and water content).

electrocardiogram (ECG), ophthalmological findings, blood chemistry or hematologic variables. No target organ for toxicity could be identified.

For detailed information refer to the BL-8040 Investigator's Brochure (IB).

1.2.1.2 Clinical Studies and Safety profile BL-8040

BL-8040 has demonstrated safety and initial clinical efficacy in three completed Phase I and II studies:

- A Phase IIa, open-label, single ascending dose, safety study of BL-8040 in combination with granulocyte colony-stimulating factor (G-CSF) in MM subjects (BKTSC001).
- A Phase IIa, multicenter, open-label study to evaluate the safety and efficacy of escalating doses of BL-8040 in subjects with relapsed/refractory AML (NCT01838395; BL-8040.01).
- A Phase I, two-part study exploring safety, tolerability, PD and PK effect of ascending doses of BL-8040 in healthy subjects (BL-8040.02).

The most frequent AEs seen in these studies were injection site reactions, including: pain, erythema, pruritus and inflammation, and systemic reactions including among others: hives, pruritus (not at the injection site), flushing, chills, rash and urticaria. Other isolated AEs reported among others were paresthesia, musculoskeletal pain, headache, constipation, tingling and elevated liver function tests.

For details concerning these studies please refer to the BL-8040 IB.

1.2.2 Atezolizumab

Atezolizumab is a humanized immunoglobulin G (IgG) 1 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 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 in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and for the treatment of metastatic non–small cell lung cancer (NSCLC).

1.2.2.1 Summary of Clinical Studies for Atezolizumab.

As of 10 May 2016, an estimated total of 6053 patients with solid tumor and hematologic malignancies have received Atezolizumab in clinical trial participation 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, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined. As of 15 December 2015, safety information was available for 629 safety-evaluable patients in Study PCD4989g, an ongoing Phase Ia trial evaluating the safety and pharmacokinetics of single-agent Atezolizumab in patients with locally advanced or metastatic solid tumors including NSCLC, urothelial carcinoma, renal cell carcinoma, triple negative breast cancer, and small-cell lung cancer and hematologic malignancies. Across all studies and tumor types, the most commonly reported adverse events with single-agent Atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough.

The adverse events observed with Atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment. Systemic immune activation, characterized by an excessive immune response, is a potential risk associated with Atezolizumab when used in combination with another immunomodulating compound.

Immune-related 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-related adverse events are closely monitored during the Atezolizumab clinical program. To date immune-related adverse events associated with Atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis. Overall most of the immune-related adverse events observed with Atezolizumab have been mild and self-limiting. Immune-related 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-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The data on development of graft-versus-host disease (GVHD) following anti-PD-L1 therapy like Atezolizumab and subsequent bone marrow transplant are limited. Given the mechanism of action of anti-PD-L1 agents as modulators of the immune system, the potential exists for acute GVHD in a patient who received treatment with Atezolizumab and then proceeded to allogeneic stem cell transplant (allo SCT).

For details concerning previous nonclinical and clinical experience, please refer to the Atezolizumab IB.

1.3 Study Rationale

The rationale to use BL-8040 is provided by data obtained by administration of growth factors in the treatment of AML. Sensitization of leukemic cells with hematopoietic growth factors, such as G-CSF and granulocyte macrophage (GM)-CSF, led to increased cytotoxicity of chemotherapy (Estey EH et al., 2001). The large study groups (HOVON and SAKK) showed that priming with G-CSF resulted in a significantly better DFS, and in the intermediate-risk group also a significantly better OS (Löwenberg B et al., 2003).

Emerging data have highlighted the importance of the BM niche for AML growth (Giles FJ et al., 2002, Mayani H, 1996, Bradstock KF et al., 1995, Liesveld JL et al., 1994). The interaction of malignant blasts with the BM micro-environment, mediated through the chemokine receptor CXCR4 and various adhesion molecules including VLA-4 and CD44, is postulated to function as a "tumor survival factor," promoting tumor growth and protecting malignant cells from chemotherapy-induced apoptosis (Bradstock KF et al., 1995, Liesveld JL et al., 1994, Matsunaga T et al., 2003, Becker PS, 2012, Bendall LJ et al., 1998). A recent clinical trial investigating AMD3100 (plerixafor) in combination with chemotherapy in patients with relapsed AML, observed leukemic cell mobilization, resulting in an overall response rate higher than expected in patients with advanced AML (Uy GL et al., 2012).

In our study BL-8040.01, the combination of BL-8040 with high dose Ara-C in patients with relapsed/refractory AML was explored. Robust mobilization of AML cells from the BM to the peripheral blood was observed, thereby sensitizing these cells to the Ara-C chemotherapy. In addition, BL-8040 had a direct apoptotic effect on the leukemia cells in the BM and induced leukemia progenitor cells towards differentiation, as evidenced by a decrease in the number of these progenitor cells. Taken together, the addition of BL-8040 resulted in an overall response rate greater than those historically expected with Ara-C alone (manuscript in preparation).

Animal studies have demonstrated that the PD-1/PD-L1 pathway plays an important role in limiting the host immune response against hematologic malignancy (Zhang L et al., 2009). PD-1–expressing T cells found in the liver of AML-bearing mice at a late stage of tumor progression have been shown to be functionally impaired and disruption of the interaction between PD-1 and PD-L1 reduced immunosuppression and restored T cell function (Zhou Q et al., 2010). Furthermore, PD-L1 has been identified as an immunoescape molecule in blast cells from patients with AML. Expression of PD-L1 increases on leukemic blast cells with relapse, therefore increased expression may be targeted to facilitate T-cell-mediated killing (Berthon C et al., 2010).

Clinical trials with PD-1 inhibitors in patients with hematologic malignancies are ongoing with promising clinical responses (Sehgal A et al., 2015). In this context, co-expression of multiple inhibitory receptors on hematopoietic cells offers the opportunity for combined blockade of specific targets/pathways to increase therapeutic efficacy. More specifically, the chemotherapy induced upregulation of PD-1 on T-cells after conventional leukemia therapy creates a solid rationale for using checkpoint inhibitors as maintenance therapy after initial chemotherapy.

The pro-apoptotic activity of BL-8040 combined with its ability to mobilize cancerous blasts from the BM to the periphery, together with Atezolizumab-induced blockade of the interaction between PD-L1 with PD-1 and CD80, might have a beneficial effect on MRD status. Specifically, this combined approach could conceivably convert a patient with MRD positive status to MRD negative status, with a positive effect on disease outcome in AML patients in CR1 that are not candidates for allogeneic stem cell transplantation. Our study regimen, offering a maintenance approach in this variable outcome group, aims at further prolonging the period of CR and thereby prolonging relapse free survival RFS.

1.3.1 Intended study

According to the above-mentioned rationale, the proposed study is planned to combine BL-8040 and Atezolizumab maintenance therapy in AML patients who are ≥18 years old in CR1 and with positive MRD. The study will assess safety, tolerability and preliminary efficacy of a treatment combination comprising BL-8040 administration on Days 1, 2 and 3 of each 21-day cycle and IV administration of Atezolizumab on Day 2 of each cycle. Treatment duration will be 2 years (a maximum of 34 cycles), until early discontinuation for any reason or until relapse, whichever comes first. Patients must be older than 18 years, diagnosed with AML (except

AML M3), and be in CR1 (including CRi, confirmed by BM) with MRD positive status. Patients will be included after a maximum of 2 cycles induction chemotherapy containing at a minimum Ara-C (may also include an anthracycline or mitoxantrone) and one or up to four cycles of Ara-C based consolidation treatment. The primary study endpoint will be safety and tolerability of the combination treatment, Atezolizumab and BL-8040. The secondary study endpoints will be RFS, assessed from CR to the occurrence of the earlier relapse or death from any cause, change in MRD, OS, and EFS. Exploratory endpoints will include among others: evaluation of the biomarkers that may serve as surrogates or predictors for clinical efficacy (analyses may include PD-L1 expression, CXCR4 expression, and presence of immune cells); evaluation of the immune response to the study drugs; analysis of presence of ADAs during the study relative to the presence of ADAs at baseline, measurement of mast cell activation. Additional molecular tests may be assessed by emerging literature and other clinical trials.

1.4 Dose Selection Rationale

1.4.1 Rationale for BL-8040 Dose Selection

In the Phase I/IIa study BKTSC001 (NCT01010880), a dose escalation study to assess the safety of BL-8040 for induction of mobilization of progenitor and stem cells from the BM to the PB in subjects with multiple myeloma, a total of 18 subjects were exposed to escalating doses according to the following scheme:

Group dose	BL-8040 mg/kg [free base]	N
1	0.006 [0.0048]	2
2	0.03 [0.024]	4
3	0.1 [0.08]	4
4	0.3 [0.24]	4
5	0.9 [0.72]	4

In Phase I study, BL-8040.02 (NCT02073019), the safety, tolerability, pharmacodynamic and PK effect of ascending doses of BL-8040 were assessed in healthy subjects. The study had two phases, escalation and expansion. A total of 26 subjects were exposed to escalating doses of BL-8040 according to the following scheme:

Group dose	BL-8040 mg/kg (free base)	N (escalation)	N (expansion)
1	0.5	8 (6 active)	-
2	0.75	8 (6 active)	-
3	1.0	8 (6 active)	8

In addition, ascending doses of BL-8040 were assessed in the BL-8040.01 (NCT01838395) study, a phase IIa study to assess the safety and efficacy of BL-8040 in subjects with relapsed/refractory acute myeloid leukemia. A total of 25 subjects were exposed to seven days of BL-8040 according to the protocol's escalation scheme and three additional subjects received compassionate use therapy according to the scheme below. All doses were found to be safe and well tolerated and the 1.5 mg/kg was selected for the currently ongoing expansion phase.

Group dose	BL-8040 mg/kg (free	N (escalation)	Compassionate
1	0.5	3	-
2	0.75	3	-
3	1.0	6	-

4	1.25	4	2
5	1.5	6	1
6	2.0	3	-

The MTD in humans for BL-8040 has not been reached. A similar PK profile was observed across different clinical studies showing similar exposure between healthy volunteers, multiple myeloma subjects and AML subjects. Adequate receptor occupancy was confirmed from the 1.0 mg/kg dose and higher. The rationale for the suggested combination relies on the ability of BL-8040 as a CXCR4 antagonist to mobilize immune cells from the BM and the lymph nodes to the PB. Rapid and dose-dependent mobilization of WBCs was seen in both, preclinical studies (mice) and humans treated with BL-8040. BL-8040 induces rapid (2-4 hrs), dose-dependent and transient mobilization of WBCs, including monocytes, B cells, T cells and NK cells. The mobilization effect of BL-8040 was observed at doses of 0.5-2.0mg/kg in all conducted clinical trials. In addition, immune suppression by the tumor microenvironment involves the production of the chemokine, CXCL12 the ligand of CXCR4, by the fibroblastic stromal cells. Binding of CXCL12 by T cells results in their exclusion from the vicinity of the cancer cells. T cell exclusion occurs in several types of human adenocarcinomas, causes antagonists of T cell checkpoints to be ineffective, despite the presence of cancer-specific CD8+ T cells. This immune suppression may be interrupted by administering BL-8040, an inhibitor of CXCR4, the receptor for CXCL12, which leads to the rapid accumulation of T cells among cancer cells, thereby uncovering the efficacy of the anti-PD-1 and eliminating cancer cells. The effect was seen in mice at a dose range of 10-20 mg/kg, equivalent to 0.83-1.66 mg/kg, respectively, in humans.

Although the higher dose tested in the BL-8040.01 study (escalation to 2 mg/kg and expansion of 1.5 mg/kg) in combination with cytarabine was found to be safe and well tolerated and MTD was not achieved, our policy with new combinations is to leave safety margins and use a dose lower than the highest tested exposure in humans. In general, BL-8040 at the dose of 1.25 mg/kg was observed to be associated with a favorable safety profile with the most common AEs being injection site irritation, flushing, and itching, and systemic reactions that were successfully managed with pre-medication. Based on the above safety and mobilization the 1.25 mg/kg dose was selected for the combination study. After treatment of 6 patients in the study, the DMC will review data and advise whether to continue with the current combination, expand the DLT period revision to assess 12 patients or whether findings suggest that changes to the dose regimen are warranted. In case 5 out of the 6 of the first patients do not experience a DLT the recruitment will not stop (as two DLT in the first 6 patients will not have been reached) and the DMC will review the safety data without stopping recruitment.

1.4.2 Rationale for Atezolizumab Dose Selection

The dose of Atezolizumab is the same across studies as a single agent and in several combinations. Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 2 of each 21-day cycle), which is the approved dosage for Atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of Atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary Study Objective - Safety and tolerability:

To demonstrate that the proposed combination is safe and tolerable.

Secondary Study Objectives:

- To assess the relapse free survival (RFS) time in patients treated with the combination of BL-8040 and Atezolizumab.
- To demonstrate that the combination of BL-8040 and Atezolizumab reduces the Minimal Residual Disease (MRD) as compared to baseline.
- To assess the Overall Survival (OS) time in patients treated with the combination of BL-8040 and Atezolizumab for maintenance.
- To assess the Event Free Survival (EFS) time in patients treated with the combination of BL-8040 and Atezolizumab for maintenance.
- To assess the time to first relapse in patients treated with the combination of BL-8040 and Atezolizumab for maintenance.

2.2 Study Endpoints/Outcome Measures

2.2.1 Safety and Tolerability Primary endpoints and Outcome Measures

- Dose Limiting Toxicity (DLT).
- Adverse Events and serious adverse events.
- 12-Lead ECG.
- Vital Signs.
- Safety laboratory tests.
- Early discontinuations; reasons and time to event.

2.2.2 Secondary Endpoints – Efficacy Measures

- Time from CR to the occurrence of earlier relapse or death from any cause (RFS).
- Change from baseline to Cycles 3, 9, 18 and 34 in MRD status measured using quantitative, multi-color, flow cytometry.
- Time from 1st study drug administration to death from any cause (OS).
- Event Free Survival (EFS) measured as the earlier from 1st study drug administration to the date of primary refractory disease, or relapse from CR, or death from any cause from 1st study drug administration.
- Relapse Free Survival (RFS).

2.2.3 Exploratory Outcome Measures

- Biomarkers that may serve as surrogates or predictors of clinical efficacy (PD-L1 expression, CXCR4 expression, and presence of immune cells).
- Immune response to BL-8040 and Atezolizumab.
- Presence of ADAs during the study relative to the presence of ADAs at baseline.
- Pharmacodynamic endpoints.
- Measurement of mast cell activation
- Molecular tests may be assessed following emerging public domain literature and other clinical trials with BL-8040.

2.2.4 Pharmacokinetic (PK) Assessment.

Sparse samples will be collected for PK analysis and to compare exposure in this study with that attained in previous studies. Serum concentrations of Atezolizumab and plasma concentrations of BL-8040 will be reported as individual values and summarized (mean, SD, coefficient of variation [%CV], median, range, geometric mean, and geometric mean CV [%CV]) by cycle, when appropriate and as data allow. Atezolizumab or BL-8040 concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution and AUC, as warranted by the data.

3 STUDY DESIGN

This is a single arm, open label, Phase Ib/II study in which eligible subjects will receive maintenance treatment consisting of intravenous (IV) infusion of 1200 mg Atezolizumab on Day 2 of each 21-day cycle and subcutaneous (SC) injections of BL-8040 (1.25mg/kg) on Days 1, 2 and 3 of each 21-day cycle. Cycles will be repeated for up to 2 years (a maximum of 34 treatment cycles), until early discontinuation for any reason or disease relapse, whichever comes first.

Patients in CR1 will be recruited after induction, with 1-4 cycles of subsequent cytarabine-based consolidation therapy, unless they have been deemed intolerant or refused to receive consolidation therapy or they received treatment with at least 3 cycles of HMA

The study will recruit an initial Risk-Benefit period staggered cohort for up to 12 subjects in order to establish the safety tolerability and efficacy of the combination treatment before opening enrollment to the full study population. Safety data will be reviewed by an independent Data Monitoring Committee (DMC) (see below for more details).

Hematology (CBC) assessment will be performed before each dose of BL-8040. BL-8040 injections will be skipped in case of a significant increase in white blood cells (WBCs) (WBC

≥ 60,000/μL) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis. Dosing will resume when the WBC count is < 60,000/μL measured before administration of BL-8040. Missed doses can be skipped until the WBC count has decreased to < 60,000/μL. up to 2 Cycles. Missed doses will not be made up if >72 h have passed. If the delay is beyond the 2 Cycles, the Medical Monitor should be consulted in order to assess the continuation of the study for the specific subject. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥60,000/μL.

3.1 Dose-Limiting Toxicities and Ongoing Safety Assessment

Adverse events (AEs) will be reported from the time of informed consent until 30 days after the last dose of study drug. The period considered for dose-limiting toxicity (DLT) assessment will be limited to the first cycle of therapy defined as the time from the first dose of BL-8040 up to and including the day when the first cycle of combination therapy ends (usually Day 21). Beyond the DLT assessment period, AE data will be collected on an ongoing basis and recorded within the CRF. However, these events will not be considered for DLT evaluation.

Dose-limiting toxicity (DLT) is defined as a clinically significant adverse event (AE) or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the first treatment cycle that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematological NCI common terminology criteria that are CTCAE Grade 3 or 4
- Change from baseline to Grade 4 neutropenia or thrombocytopenia lasting for >4 weeks in the absence of persistent leukemia.
- Symptomatic leukostasis

To be considered a DLT the toxicity must be possibly, probably or definitely related to either of the study drugs or the combination.

An AE must be clinically significant to define a DLT, e.g., nausea and vomiting, alopecia, study drug-related fever or electrolyte abnormalities that are ≤ grade 3 will not constitute DLT. For subjects who experience a DLT, the study continuation should be discussed with the Medical Monitor. Subjects who experience AEs that are not considered DLT or are unrelated to BL-8040 or Atezolizumab may continue study participation at the discretion of the Investigator.

BL-8040 injections may be skipped for any reason per Investigator judgment; however, they must be skipped in the case of a WBC >60,000/μL, measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis.

Increase in WBC is not considered a DLT since it is a direct effect of CXCR4 inhibition and reflects the drug's mechanism of action.

In case of elevated WBC > 60,000/μL, daily WBC assessment should be done, and BL-8040 treatment can be resumed provided that the WBC counts decrease to ≤ 60,000/μL. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥40,000/μL. For values <40,000/μL daily WBC monitoring may be stopped and further analysis should be done based on the Investigator's judgment.

The study will consist of two periods:

- Initial Risk-Benefit period which will enroll a total of 12 subjects. The decision whether to continue the extension phase will be made based on a risk-benefit analysis and data review by the DMC together with the Sponsor.
- Expansion period of up to 48 additional patients.

Safety review of the accumulated data will be performed by an independent DMC after the first 6 patients have completed the first cycle of combination therapy and further again after 6 additional patients have completed the first cycle of combination therapy. Guidelines to be used by the DMC for the review of the proposed combination toxicity are presented below:

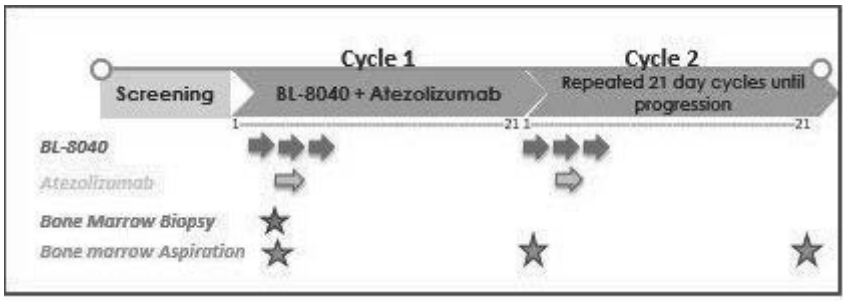
- If ≤1 out of 6 subjects experiences a DLT during the first cycle of treatment, enrolment should be continued to include 6 additional patients.
- If ≥ 2 out of 6 subjects experience a DLT, the DMC will assess the risk/benefit profile of the combination treatment and recommend one or more of the following: 1) Recruitment should be continued to include 6 additional patients 2) the protocol should be modified 3) the treatment schedule should be modified 4) the study should be discontinued.
- If ≤ 2 out of 12 subjects experience a DLT the DMC will recommend a recruitment of additional 3 subjects for the completion of the pre-planned Initial Risk-Benefit Period population size of 12 subjects., the DMC will recommend one or more of the following:
- If > 2 out of 12 subjects experience a DLT the DMC will recommend one or more of the following: 1) Recruitment should be continued to include 3 additional patients for the completion of the pre-planned Initial Risk-Benefit Period population size of 12 subjects, 2) the protocol should be modified, 3) the treatment schedule should be modified or 4) the study should be discontinued. Following the completion of this initial risk-benefit period which is planned to enrol a total of 12 patients, an integrative analysis of risk-benefit of the proposed combination will be performed. Then the DMC, jointly with the sponsor, based on an assessment of the integrated database will decide whether to continue to the expansion period and to enrol additional 48 patients or to early discontinue the study.

The number of patients planned for DLT assessment will be up to 12, recruited in a staggered manner not exceeding the potential for observing that the proposed combination therapy would be considered unacceptably toxic according to the criteria above. In order to be evaluable for the DLT assessment period, a subject must complete the first cycle of treatment. If a subject is discontinued before completion of the first cycle (unless due to a DLT), an additional subject will be recruited and included in the Safety DLT Cohort to ensure a total of six evaluable subjects. Similar rules will be applied in the expanded 12 subject cohort.

Clinical sites are required to contact the Sponsor within 24 hrs in case subjects present suspected DLTs during the assessment period.

After completion of the DLT assessment period, further DMC assessments will be performed biannually. Standard therapy event rates and toxicity measurements for these findings will be obtained from historical data reviews. Any CI that no longer covers the historical event rate or the historical mean of a continuous toxicity measurement will represent a possible increase in the risk/benefit profile for the subjects. These data will be presented to the DMC for review. The DMC will be charged with monitoring the performance and safety profile of the protocol for the subjects.

3.2 Study Diagram:



4 STUDY POPULATION

This study will be conducted in AML patients, aged ≥ 18 years, who are in CR1 and not planned for stem cell transplantation. Up to 60 patients are planned to be enrolled in the study.

4.1 Inclusion Criteria

1. Adult men and women aged ≥ 18 years.
2. Confirmed diagnosis of AML (according to WHO criteria. See Appendix C)
3. Subjects with newly diagnosed AML who have achieved complete remission (CR or CRi/), after
   a. Up to two cycles of cytarabine based induction chemotherapy.
   b. A minimum of 3 cycles of HMA, such as azacytidine, decitabine, etc.
4. Subjects with intermediate or adverse risk factors according to the ENL guidelines 2017[a].
5. CR (or CRi) must be confirmed by bone marrow aspirate up to 28 days prior to enrollment.
6. Subjects who have received 1-4 cycles of consolidation therapy unless they have been deemed intolerant, or have refused consolidation or, for patients that received at least 3 cycles of HMA.
7. Subjects who prior to screening are MRD positive according to the local laboratory or with an unknown MRD status; are to be confirmed or tested, respectively, for MRD by central laboratory prior to enrollment.
8. Subjects who were diagnosed with AML within 18 months prior to study enrollment.
9. Subjects should have received the last dose of the induction or consolidation or HMA, whichever comes later, therapy within 6 months prior to study enrollment.
10. Subjects who, at the time of enrollment, are not planned for allogeneic stem cell transplantation.
11. Female subjects must be post-menopausal or of non-childbearing potential defined as the absence of menses for > 1 year or those who have had a bilateral tubal ligation or hysterectomy.
12. Male subjects with partners of childbearing potential must agree to use an adequate method of contraception starting with the first dose of the study therapy through at least 5 months after the last dose of the study therapy. Examples of adequate methods are: for males- condom with or without spermicide, sexual abstinence or surgical sterility

[a] Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Döhner H. et al, Blood, 26 January 2017 X Volume 129, Number 4-Appendix F

(vasectomy) or for female partners of childbearing potential-oral, transdermal patch, implanted contraceptives, intrauterine device, diaphragm.

13. Subject is able and willing to comply with the requirements of the protocol.
14. Subject is able to voluntarily provide written informed consent prior to initiation of any study-related procedure.

4.2 Exclusion Criteria

1. Subjects diagnosed with acute promyelocytic leukemia.
2. Subjects with extramedullary AML, including CNS involvement.
3. Subjects who have achieved CR or CRi following treatment for relapsed or refractory AML after 2 inductions.
4. Subjects in CR1 following allogeneic stem cell transplantation.
5. Subjects who are candidates for allogeneic stem cell transplantation and have a suitable donor.
6. Life expectancy of ≤ 6 months.
7. Clinically significant abnormal laboratory safety test values including, but not limited to:
    - Total bilirubin > 2 times upper limit of normal (x ULN)
    - Aspartate Aminotransferase (AST/SGOT) or Alanine Aminotransferase (ALT/SGPT) > 2 x ULN
    - Creatinine > 1.5 x ULN or GFR < 30 mL/min.
8. Low Performance Status (ECOG > 2; Appendix D).
9. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor alpha [anti–TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
    - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contact allergy) are eligible for the study after Medical Monitor approval has been obtained.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
    - Requirement for use of denosumab during the study: Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study.
10. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment.
11. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with Atezolizumab or within 5 months after the last dose of Atezolizumab
12. Previous treatment with immune checkpoint blockade therapies (anti−CTLA-4, anti−PD-1, or anti−PD-L1) or immune agonists (anti-CD137, anti-CD40, anti-OX40).

13. Known allergy or hypersensitivity to any of the test compounds, materials or contraindication to test product, including:
    - History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies or fusion proteins
    - Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the Atezolizumab formulation.
14. Use of investigational device or drug within 2 weeks or five half-lives, whichever is longer, prior to the enrolment date.
15. Past or current history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune myocarditis, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover <10% of body surface area
        - The disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months.
16. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
17. Serious infection requiring oral or IV antibiotics, antifungals, antivirals, and/or hospitalization within 14 days prior to Cycle 1, Day 1
    - Patients who receive prophylactic oral antibiotics, antifungals, and antivirals as a result of prolonged neutropenia in the absence of documented infection are eligible.
    - Patients being treated for non-serious, infectious complications (e.g., oral candidiasis or uncomplicated urinary tract infection) with oral and/or topical antimicrobials may be eligible for study treatment (antimicrobials must be completed, prior to Cycle 1, Day 1 and all cases must be discussed with and approved by the Medical Monitor).
18. Subjects with a history of organ or stem cell transplantation.
19. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease and inherited liver disease.
20. Active tuberculosis.

21. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 12 months prior to initiation of study treatment, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment.
22. Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment.
23. Positive HIV test at screening or at any time prior to screening.
24. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.
25. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
26. Subjects with concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness which could place him/her at unacceptable risk, including, but not limited to:
    - History of malignancy other than AML 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.
    - Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.
    - Unable to comply with study requirements in the opinion of the Investigator.

4.3 Subject Identification

At screening, all subjects who signed informed consent will be identified by a subject number, initials and birth date; the subject number will be used throughout the study. Screening failures numbers will not be re-assigned. Subject numbers will not be re-used for different subjects.

4.4 Screening Failures

Subjects who fail to meet the entrance criteria at any stage during the screening period are defined as screen failures. All screen failures will be documented on the screening log, which documents the subject number, subject's initials, birth date and reason(s) for screen failure. The screening log will be kept in the Investigator's Site File.

Screen failure subjects will be withdrawn from the study and receive standard of care performed at the site. Subjects may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures, listed in the protocol flow chart, including re-consent signature

4.5 Removal, Replacement, or Early Withdrawal of Subjects from Therapy or Assessment

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject

requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject.

Subjects withdrawn from the study prior to first BL-8040 injection will be replaced by the Investigator to achieve the appropriate number of subjects, regardless of the reason for withdrawal.

Subjects must complete the first cycle of treatment in order to be evaluable for the DLT assessment period. If a subject is discontinued before completion of the first cycle for any reason other than a DLT, an additional subject will be recruited and included in the Safety DLT Cohort to ensure a total of six evaluable subjects. Similar rules will be applied in case the Safety DLT Cohort is expanded to 12 subjects.

The subject's participation in this study may be discontinued due to the following reasons:

- Request of regulatory agency or Sponsor or primary care physician or Investigator
- Withdrawal of consent by subject
- Any subject who develops intolerance to treatment
- Any subject who requires concomitant medication which could confound evaluation of the study drug
- The subject is unwilling or unable to continue the study or is lost to follow-up
- The subject is non-compliant with study procedures / study protocol
- Investigator decides that withdrawal from the study is in the best interest of the subject
- Subject meets one of the stopping/dosing interruption rules criteria during the study (see Sections 6.2.4 and 6.2.5).

4.6 Handling of Withdrawals

If a subject is withdrawn from the study, either at his/her request or at the Investigator's discretion or if requested by the Sponsor, primary care physician or regulatory agency, or fails to return, every effort should be made to determine the reason. This information will be recorded on the subject's case report form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo all Early Discontinuation Study Visit assessments (see Section 5.6). It is vital to obtain follow-up data for any subject withdrawn because of an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

Premature withdrawal may occur for any of the following reasons:

1. Death
2. Disease progression/relapse
3. AE
4. Subject request
5. Investigator request
6. Sponsor request
7. Other party's request
8. Any other reason

If withdrawal is caused by an AE that the Investigator considers may be related to the study drug, it will be reported to the DMC, institutional review board/independent ethics committee (IRB/IEC) and Sponsor.

Any serious AE (SAE) must be reported to the Sponsor or Sponsor's designee within 24 hours of becoming aware of the event and to the IRB/IEC according to local regulations (for SAE notification procedures, refer to Section 7.5).

In the event of any AEs considered to be clinically significant by the Investigator, subjects will be followed up with appropriate medical management until the outcome is determined or stabilized, according to the Investigator's clinical judgment. All follow-up information will be recorded in the subject's CRF until resolution of the AE. Subsequent follow-up will be documented in the subject's personal file.

4.7 Sponsor's Termination of Study

The Sponsor reserves the right to discontinue the study at any time at the participating centers for any reason included in the applicable law.

Regulatory Authorities also have the right to terminate the study for any reason.

5 STUDY PROCEDURES AND ASSESSMENTS

The schedule of events for this study is shown in Appendix A. No protocol related procedures should be performed before subjects provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study medication, and descriptions of AEs should be recorded in the appropriate source documents and CRF.

5.1 Screening Period (Visit 1, Day -28 to Day -1)

At Visit 1, the purpose and procedures of the study will be fully explained to participants. Those wishing to enroll in the study will sign a written informed consent prior to initiating any evaluations or study-related procedures. Following the signing of informed consent, adult male and post-menopausal female subjects aged ≥ 18 years will be screened for study eligibility by assessment of inclusion and exclusion criteria.

The following assessments will be performed at screening (visit 1):

- Collection of demographic data and medical history.
- Prior and concomitant medication review.
- Full physical examination (including weight measurement).

- Vital signs (blood pressure, pulse rate, oral temperature, O_2 saturation and respiratory rate).
- ECOG performance status (Appendix D).
- 12-lead electrocardiogram (ECG).
- Safety laboratory assessments including hematology, biochemistry, thyroid function tests (T3, T4 and TSH) and coagulation (PT/INR and aPTT), HCV and HBV serology.
- HIV serology, unless not permitted per local regulations
- CT scan chest (within 28 days prior to treatment).
- Fresh BM biopsy taken during the screening visit (following approval of provisional enrollment package) to confirm AML status (CR or CRi) and ENL prognostic factors.
- BM aspirate to confirm positive MRD status by central laboratory assessment and for DNA and RNA for the correlative studies (optional for Israel).
- Blood sampling for biomarker assessment including DNA and RNA for the correlative studies (optional for Israel).
- Review of inclusion and exclusion criteria.

5.2 Baseline (Pre-Dose, Day 1 of Treatment Cycle 1)

The following assessments will be performed at baseline:

- AE and concomitant medication review
- Directed physical examination (including weight measurement).
- Vital signs.
- ECOG performance status.
- 12-lead electrocardiogram (ECG).
- Safety laboratory assessments including hematology and biochemistry
- Review of inclusion/exclusion criteria and confirmation of eligibility.
- Pre-dose BL-8040 PK sample.
- Pre-dose sample for anti-BL-8040 antibodies, complement activation and biomarkers.

5.3 Treatment Period (Days 1, 2 and 3 of each treatment cycle)

During the treatment period, eligible subjects will receive study drug on Days 1, 2 and 3 of each 21-day cycle. Cycles will be repeated for up to 2 years (a maximum of 34 treatment cycles), until early discontinuation for any reason or disease relapse, whichever comes first. There will be a ± 3-day window for the start of each treatment cycle.

Subjects will receive once daily SC injections of 1.25 mg/kg of BL-8040 on Days 1, 2 and 3 of each 21-day cycle. Subjects will receive Atezolizumab 1200 mg IV on Day 2 of every cycle. The first infusion of Atezolizumab should be administered over 60 mins. If well tolerated, subsequent infusions may be performed over 30 mins. On Day 2, BL-8040 will be administered 1 h (± 30 min) after the end of the Atezolizumab infusion.

Hematology (CBC) assessment will be performed before each dose of BL-8040. BL-8040 injections will be skipped in case of a significant increase in WBCs (WBC ≥ 60,000/μL) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis. Dosing will resume when the WBC count is < 60,000/μL measured before administration of BL-8040. Missed doses can be skipped until the WBC count has decreased to < 60,000/μL, up to 2 cycles. Missed doses will not be made up if >72 h have passed.

If the delay is beyond the 2 Cycles, the Medical Monitor should be consulted in order to assess the continuation of the study for the specific subject. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥60,000/μL.

The following assessments will be performed throughout the treatment period at the time points indicated in the schedule of assessments (see Appendix A):

- Clinical Evaluations:
  - AE and concomitant medication review will be performed on every treatment day throughout the study.
  - ECOG performance status will be determined pre-dose on Day 1 of every cycle.
  - Directed physical examination will be performed pre-dose on Day 1 of every treatment cycle.
  - Subject weight will be measured pre-dose on Day 1 of every treatment cycle to determine the correct dose of BL-8040.
- Vital signs will be assessed on:
  - Days 1, 2 and 3 at pre-dose and 4 ± 2 h post-BL-8040 administration during the first cycle.
  - In the following cycles pre-dose and 4±2h post BL-8040 administration on day 1 only.
  - Additional assessments may be performed at the discretion of the Investigator or upon Sponsor's request.
- 12-lead ECGs:
  - 12-lead ECGs will be recorded on Day 1 and 2 of treatment cycle 1 at pre-dose and 4 ± 2 h post-BL-8040 administration.
  - Additional ECGs may be performed at the discretion of the Investigator or upon Sponsor's request.
- Laboratory safety evaluations:
  - Hematology (CBC) and differential counts will be performed before each dose of BL-8040 throughout the study (see above). During treatment cycle 1, samples will also be collected at 4 ± 2 h post-BL-8040 administration on day 1, 2 and 3.
  - Biochemistry samples will be collected pre-dose on Day 1 and 3 on cycle 1 and on day 1 and 3 pre-dose every cycle.
  - Thyroid function tests and coagulation will be tested pre-dose on Day 1 of every other treatment cycle starting from treatment cycle 2.
  - Additional hematology, biochemistry and coagulation samples may be collected at the discretion of the Investigator or upon Sponsor's request.
- BM Aspirate/Flow Cytometry Analysis:
  - BM aspirate samples for determination of MRD status by Flow Cytometry will be collected post dose on Day 3 of treatment cycles 3, 9, 18, end of cycle 34/end of treatment (whichever comes first).
  - Peripheral blood and BM aspirate samples for immune-phenotyping by Flow Cytometry including measuring CXCR4, PD-1 and PD-L1 as well as DNA and RNA for the correlative studies (optional for Israel) will be collected post dose on Day 3 of treatment cycles 3, 9, end of cycle 18, end of cycle 34/end of treatment (whichever comes first).
- PK Sampling: See Appendix B.
- Anti-drug Antibody (ADA) and Complement Activation

- Blood samples for assessment of BL-8040 ADA and complement activation will be collected according to timepoints listed in Appendix B.
- Blood samples for assessment of Atezolizumab ADA and complement activation will be collected according to timepoints listed in Appendix B.

o Blood Sampling for biomarkers

- Cycles 1, 3, 9 and 18. Day 1 pre-dose and day 3 2 hours post dose.
- End of treatment or discontinuation visit.

5.4 End of treatment visit (Treatment discontinuation)

An end of treatment visit will be performed at the time of treatment discontinuation. The following assessments will be performed:

- AE and concomitant medication review.
- ECOG performance status.
- Full physical examination.
- Vital signs.
- 12-lead Electrocardiogram (ECG).
- Safety laboratory assessments including haematology, biochemistry, thyroid function tests (T3, T4 and TSH) and coagulation (PT/INR and aPTT).
- Blood sample for anti-BL-8040 antibodies and complement activation and anti-Atezolizumab antibodies
- Peripheral blood and BM aspirate samples for DNA and RNA for correlative studies (optional for Israel).
- Post-study anticancer therapy status.

5.5 Follow-Up visit

Follow-up is divided into 2 parts:

- A safety follow-up for 30 days after treatment discontinuation, or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. The safety follow-up period may be extended up to 90 days after the last dose of study drug for any SAEs considered reasonable possibly related to BL-8040 and/or Atezolizumab.
- Long term survival follow-up every 3 months (± 1 month) and up to 5 years.

During both the survival follow-up, the following assessments will be performed:

- Post-study anticancer therapy status
- Relapse and survival status (patients who discontinue the study for any reason e.g. relapse, personal decision.

5.6 Early Discontinuation Study Visit

An early discontinuation study visit will be performed for subjects who withdraw from the study for the reasons specified in Section 4.5.

All reasons for treatment discontinuation will be documented in the source documents as well as in the CRF. Only one reason (the most severe) for early discontinuation should be recorded in the CRF. If one of the reasons for discontinuation is an AE, this should be chosen as the reason. Every effort should be made to follow-up these subjects for resolution of the AE.

This visit may be performed on the same day as an originally scheduled visit or could be conducted separately. The data collected at this visit should be as listed in Section 5.6.

5.7 Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not be limited to) laboratory safety tests, vital signs and physical examination.

5.8 Safety Assessments

Safety assessments will be based on changes from baseline of clinical signs and symptoms reported by the subject or observed by the Investigator, including AEs, concomitant medication use, treatment compliance, tolerability (e.g., dropouts due to AEs), vital signs, ECGs, physical examination and laboratory safety assessments.

5.8.1 Adverse Events (AEs)

Adverse Events will be assessed at all study visits from the date of informed consent and throughout the entire study until the end of the safety follow up.

Any new systemic AE that occurs between scheduled assessment visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate CRF page.

AEs will be reported and graded in accordance with the latest NCI-CTCAE version (currently version 4.03) and coded by Data Management using the latest version of MedDRA (currently version 19.0) (see Section 7.1 for more details).

5.8.2 Concomitant Medications

Concomitant medication use will be recorded from baseline (visit 2) through all study visits. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included in the CRF.

Vital signs will be measured at the time points indicated in the schedule of assessments (see Appendix A). Vital signs will include blood pressure, pulse rate, oral temperature, oxygen saturation and respiration rate after at least 5 min rest as per standard practice at the investigational site. Significant findings noticed after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

5.8.3 Electrocardiogram

Electrocardiograms will be performed at the time points indicated in the schedule of assessments (Appendix A). Additional 12-lead ECGs may be performed at the discretion of the Investigator or upon Sponsor request. The subject should rest for at least 10 minutes before measurements are taken.

ECG printouts will be evaluated by the Investigator or designee, signed and dated and filed in the source documentation file. When potentially clinically significant findings are detected by the Investigator or designee, a cardiologist should be consulted for a definitive interpretation and appropriate treatment, if required. All communications and diagnoses should be filed in

the source documentation file and clinically significant findings should be reported within the CRF. The Investigator/Investigator's designee/local cardiologist is responsible for determining whether the ECG findings are of clinical significance. All abnormalities will be closely monitored until stabilized or resolved.

5.8.4 Physical Examination

A full physical examination will be conducted at screening (visit 1), and at the end of treatment visit.

Physical examination will include weight measurement, assessment of head, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, neurological system and, where appropriate, other body systems as indicated in the study schedule.

A directed physical examination will be performed on Day 1 of each treatment cycle.

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the signature of the informed consent must be included in the Relevant Medical History/ Current Medical Conditions CRF. Significant findings made after the signature of the informed consent which meet the definition of an AE must be recorded on the AE CRF module.

5.8.5 Vital signs

Vital signs will be measured at the time points indicated in the schedule of assessments (Appendix A).

Vital signs will include blood pressure, pulse rate, oral temperature, oxygen saturation and respiration rate after at least 5 min rest as per standard practice at the investigational site. Significant findings noticed after the start of study drug which meet the definition of an AE must be recorded on the AE CRF module.

5.8.6 Laboratory Safety Assessments

Laboratory safety sampling will include the parameters listed below. The exact time-points for each one of the tests are specified in the schedule of assessments (Appendix A).

Evaluations	Parameters
Hematology	Red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential (including number of blasts, neutrophils and lymphocytes) and platelet count.
Biochemistry	Electrolytes: sodium, chloride, potassium, calcium and phosphorus Liver function tests: AST (not mandatory and only upon ALT elevation), ALT, ALP, total bilirubin, direct bilirubin, total protein, albumin Kidney function tests: creatinine, BUN Other: glucose, uric acid
Coagulation	Pro-thrombin time (PT)/INR and activated partial thromboplastin time (aPTT)
Serology[a]	HIV antibodies (HIV1 and HIV2), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibody (Hep C Ab).
Other	Thyroid function tests (T3, T4 and TSH)

[a] To be collected at screening only.

Laboratory safety test abnormalities, which arise after study drug administration, will be repeated as clinically indicated until the values return to normal or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the AE CRF module.

A laboratory abnormality will not be considered an AE unless:

- Intervention is required
- Changes in dose are required (decrease, discontinued, interrupted)
- Other treatment/therapy is required
- Associated with other diagnoses
- Is considered clinically significant by the investigator

Laboratory results will be reported to the Investigator or designee who will review, sign and date abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern or values that were outside normal ranges and provide details of the relationship to investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) in addition to the actual value will be recorded.

5.8.7 Anti-drug antibody (ADA) Assessment

Blood sampling for assessment of ADA formation and complement activation will be performed at the time points indicated in the schedule of assessments (Appendix A).

5.9 Biomarker and Pharmacodynamic Assessments

5.9.1 MRD Status

MRD status will be determined by flow cytometry analysis of BM aspirates collected at the time points indicated in the schedule of assessments (Appendix A). MRD assessments will be performed at a central laboratory. According to the assay used, any level of detectable MRD is considered positive.

5.9.2 Immuno-phenotyping

Immuno-phenotyping and PD-1/PD-L1 and CXCR4 expression will be performed on peripheral blood and BM aspirates collected at the time points indicated in the schedule of assessments (Appendix A).

5.9.3 DNA and RNA Collection

DNA and RNA collection will be performed on peripheral blood and BM aspirates collected at the time points indicated in the schedule of assessments (optional for Israel) (Appendix A).

5.9.4 PK Assessments

PK sampling schedule is listed in Appendix B.

PK analysis of BL-8040 will be conducted by BioLineRx using a validated High-Performance Liquid Chromatography (HPLC) method. Serum concentration of Atezolizumab will be analyzed with a validated ELISA assay.

5.9.5 Blood Sampling and Processing

Samples will be collected for safety and efficacy analysis, ADA titers and determination of BL-8040 plasma concentrations at the time-points indicated in Appendix A.

Instructions for the collection, processing, storage and shipment of samples are detailed in the Laboratory Manual provided by the Sponsor.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Products

6.1.1 BL-8040

BL-8040 is a highly selective CXCR4 antagonist co-developed by [redacted]. and BioLineRx Ltd. as a novel investigational therapy for the treatment of cancer.

BL-8040 drug product is formulated as a sterile and non-pyrogenic lyophilized powder for reconstitution in a vial containing 73mg BL-8040 free base peptide, on dry basis. BL-8040 administrated SC upon reconstitution with 2mL 0.45% Sodium Chloride for Injection (Half Normal Saline). BL-8040 is filled and packed in clear Type I glass vials (DIN 6R) with 20mm rubber stoppers and sealed with 20mm aluminum caps.

6.1.2 Atezolizumab

The Atezolizumab drug product will be supplied by the Sponsor in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of Atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

6.2 Study Drug Administration and Dosage

6.2.1 BL-8040

Subjects will receive once daily SC injections of 1.25 mg/kg of BL-8040 on Days 1, 2 and 3 of each 21 day-cycle.

The BL-8040 injection site will be rotated daily, to minimize the severity of local injection site reactions. When volume after reconstitution is greater than 2 mL the injection should be split. At the discretion of the Investigator, lower volumes may be split and injected into more than one site. When the dose is split, the injection should be applied at various parts of the body, e.g. arm and leg

Hematology (CBC) assessment will be performed before each dose of BL-8040. BL-8040 injections will be skipped in case of a significant increase in WBCs (WBC $\geq$ 60,000/μL) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis. Dosing will resume when the WBC count is < 60,000/μL measured before administration of BL-8040. Missed doses can be skipped until the WBC count has decreased to < 60,000/μL, up to 2 cycles. Missed doses will not be made up if > 72 h have passed. If the delay is beyond the 2 Cycles, the medical monitor should be consulted in order to assess the continuation of the study for the specific patient. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥60,000/μL.

6.2.2 Atezolizumab

Subjects will receive Atezolizumab 1200 mg IV on Day 2 of every cycle. The first infusion of Atezolizumab should be administered over 60 mins. If well tolerated, subsequent infusions

may be performed over 30 mins. On Day 2, BL-8040 will be administered 1 h (± 30 min) after the end of the Atezolizumab infusion.

Administration of Atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix F. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the first Atezolizumab administration. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded 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 recorded during the infusion and at 30 (± 5) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.
Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix F.
No dose modification for Atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in sections 6.2.4-6.2.7.

6.2.3 Dose Limiting Toxicities

Dose-limiting toxicity (DLT) is defined as a clinically significant AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the first treatment cycle that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematologic NCI common terminology criteria that are CTCAE grade 3 or 4

- Change from baseline to Grade 4 neutropenia or thrombocytopenia lasting for >4 weeks in the absence of persistent leukemia.
- Symptomatic leukostasis

To be considered a DLT the toxicity must be possibly, probably or definitely related to either of the study drugs or the combination.

An AE must be clinically significant to define DLT, e.g., nausea and vomiting, alopecia, study drug-related fever or electrolyte abnormalities that are ≤ grade 3 will not constitute DLT. For subjects who experience a DLT, the study continuation should be discussed with the Medical Monitor. Subjects who experience AEs that are not considered DLT or are unrelated to BL-8040 or Atezolizumab may continue study participation at the discretion of the Investigator.

BL-8040 injections may be skipped for any reason as per Investigator judgment; however, they must be skipped in the case of a WBC >60,000/μL, measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis.

Increase in WBC is not considered a DLT since it is a direct effect of CXCR4 inhibition and reflects the drug's mechanism of action.
In case of elevated WBC > 60,000/μL, daily WBC assessment should be done, and BL-8040 treatment can be resumed provided that the WBC counts decrease to ≤ 60,000/μL. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥40,000/μL. For values <40,000/μL daily WBC monitoring may be stopped and further analysis should be done based on the Investigator's judgment.

6.2.4 BL-8040 Treatment Interruption Rules

For subjects experiencing ≥ grade 3 BL-8040 related toxicity, the study continuation will be discussed with a Medical Monitor. Patients who discontinue from a study due to any AE, will be followed for until resolution or stabilization of toxicity. Subjects who experience any toxicity, which is not related to BL-8040 will be allowed to continue BL-8040 treatment at the Investigator's discretion.

BL-8040 injections will be stopped in case of a persistent, significant increase in WBC (WBC ≥ 60,000/μL) measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis or grade 3-4 allergic reaction. These subjects will be withdrawn from the study and will be followed-up for safety for up to 90 days.

6.2.5 Atezolizumab Treatment Interruption Rules

Atezolizumab IV infusions must be withheld in the event of for any of the following events:

- Grade 2 pneumonitis
- AST or ALT > 3 and ≤ 5 times ULN, or total bilirubin > 1.5 and ≤ 3 times ULN
- Grade 2 or 3 diarrhea or colitis
- Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or grade 3 or 4 hyperglycemia
- Grade 2 ocular inflammatory toxicity
- Grade 2 or 3 pancreatitis, or grade 3 or 4 increases in amylase or lipase levels (> 2 times ULN)
- Grade 3 or 4 infection
- Grade 2 infusion-related reactions
- Grade 3 rash.
- Grade 2 Immune related myocarditis and neuropathy

6.2.6 Atezolizumab Re-introduction

Atezolizumab IV infusions may be resumed in patients whose AEs recover to grade ≤ 1.

6.2.7 Permanent Discontinuation of Atezolizumab

Atezolizumab IV infusions must be permanently discontinued in the event of any of the following events:

- Grade 3 or 4 pneumonitis
- AST or ALT > 5 times ULN or total bilirubin > 3 times ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Myasthenic syndrome/myasthenia gravis, Guillain-Barré, or meningoencephalitis (all grades)
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent pancreatitis
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash
- Grade 3 or 4 Immune related myocarditis and neuropathy

6.2.8 Atezolizumab Dose Reduction

No Atezolizumab dose reductions are recommended.

6.2.9 Rescue medication

Rescue medication regimens will be applied according to the respective clinical conditions at the discretion of the Investigator.

6.3 Manufacturing of Study Medication

6.3.1 BL-8040

BL-8040 drug substance (4F-benzoyl-TN14003 peptide) is a white or off-white powder synthetic polypeptide, freely soluble in water and in 0.45% Sodium Chloride (half normal saline). It is manufactured in accordance with current good manufacturing practice (cGMP) requirements by [redacted]
Reconstitution and administration instructions will be provided in the Pharmacy Manual.

6.3.2 Atezolizumab

The Atezolizumab drug product is provided in a single-use, 20-cc USP or European Pharmacopoeia Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the Atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

6.4 Packaging and Labeling of Study Medication

6.4.1 BL-8040

The study drug is packaged in a USP Type 1 clear glass, single-use, 6 mL vial. The packaging and labeling will be performed by:

[redacted]

Steinbuhlweg 69
[redacted]For information on the formulation and handling of BL-8040, see the pharmacy manual and the BL-8040 Investigator's Brochure.

6.4.2 Atezolizumab

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

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

6.5 Distribution and Shipment of Study Medication

The investigational medicinal product will be packed and shipped in appropriate boxes. If, upon arrival at the clinical investigation site, study drug supplies appear to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, product certificate of analysis, acknowledgement of receipt and other appropriate documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply to the study monitor.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. The Sponsor or its representative must notify the Principal Investigator's designee prior to dispatch of drug supplies, with the anticipated date of their arrival.

6.6 Storage, Dispensing and Return of the Investigational Medicinal Products

Vials of BL-8040 for injection should be stored in the refrigerator (2-8°C) in its original packaging, protected from light.

Vials of Atezolizumab should be stored according to the instructions provided in the Pharmacy Manual.

Records should also be kept by the Investigator or designee as to how much study drug was dispensed to each subject. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug, and be sure that drug accountability is being performed at each visit, and the drug accountability logs are maintained.

All investigational products must be kept in a secure area with access to the study drug limited to designated study personnel.

Only trained personnel under the supervision of either the Investigator or the local pharmacist are authorized to dispense and administer study drug to participating subjects.

Further details and instructions will be provided in the Pharmacy Manual.

6.7 Accountability and Compliance of Investigational Medicinal Product

Each delivery must be acknowledged by the hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form and returning it by fax/email to the Sponsor or designee. Accurate, complete and timely

documentation of study drug distribution will be maintained by the pharmacy and the study staff of the investigational site which may include confirmation of receipts of clinical supply, drug accountability logs and other forms.

The medical center pharmacist (or authorized study team member responsible for the investigational medicinal product) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator may dispense investigational drug only to subjects enrolled in the study.

Drug accountability records must be maintained by the clinical investigation site at all times. At the last study visit, all used and unused investigational drug will be collected and drug accountability performed by the study staff. The study monitor will check these regularly during monitoring visits.

The subject number, the date, batch number/pack number and quantity of study drug used by the subject will be checked for correctness and recorded on the appropriate accountability forms. Unused drug supplies will be returned to the Sponsor. At the end of the study, all clinical supplies and the corresponding accountability forms must be returned to the Sponsor, the study monitor, or designee for reconciliation or destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study.

Compliance:

For subjects that will have to skip two consecutive cycles due to any reason the decision to continue the participation in the study should be discussed with the Medical Monitor.

6.8 Concomitant Therapy

At the screening visit, relevant treatments currently received by the subject will be recorded in the subject's CRF including treatment's name, indication, dose, total daily dose and start and stop dates.

Any medications (including prescription, over-the-counter, herbal supplements and other health store-type products) to be taken during the study must be approved by the Investigator.

All concomitant medications received within 30 days prior to the screening visit and 30 days after the last dose of trial treatment should be recorded. The following information should be recorded: treatment's name (generic, if possible), indication, dose and start and stop dates. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included in the CRF. All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded when related to SAEs.

Transient hypotension was witnessed in several cases following the initial treatment with BL-8040. Therefore, caution should be taken with the use of negative chronotropic drugs such as

beta blockers. When appropriate, beta blocker should be replaced by non-negative chronotropic alternatives.

6.8.1 BL-8040 Adverse Event Management:

- *Premedication* prior to BL-8040 injection with antihistamines (e.g. diphenhydramine, promethazine, etc.) in order to minimize the occurrence of BL-8040 related systemic reactions is highly recommended.
- Systemic steroids are allowed for the treatment of systemic reaction but not as regular pre-medication of these reactions.
- Clinically appropriate measures in case of BL-8040-related local injection site reactions e.g., local corticosteroids, systemic and local painkillers, antihistamines, local treatments etc.

6.8.2 Permitted Concomitant Medications

The following concomitant medications/therapies will be allowed during the treatment period:

- Antiemetic drugs (e.g., Ondansetron) as required clinically based on local guidelines for subjects experiencing nausea.
- Prophylactic antibiotics (e.g., quinolone or cephalosporin), anti-fungals (e.g., voriconazole) and antivirals (e.g., valacyclovir) when appropriate.
- Blood products, commonly required in oncology subjects.
- Low-dose steroids are allowed as pre-medication for blood transfusion or with IV anti-fungals.
- Vitamins, nutritional supplements, herbal supplements and over the counter medications are permitted per PI's judgement.
- Vitamin D therapy.
- Polyphenols in green tea/supplements.

Additional medications/therapies to manage treatment or disease emergent conditions will be allowed at the discretion of the Investigator in consultation with the Sponsor, in advance when possible. In case there is a change in therapy related to an AE, the Sponsor or Investigator may decide to withdraw the subject (refer to Section 4.6).

6.8.3 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the screening period and treatment phase of this trial:

- Other treatment for their AML
- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy or other therapy not specified in this protocol.
- Investigational agents other than BL-8040 and Atezolizumab.
- Lodonal
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial and 5 months after the last dose of Atezolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus and are allowed. However, intranasal

influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines and are not allowed. No live attenuated vaccines can be given up to 5 months post last dose.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or for systemic and local reactions secondary to BL-8040 and/or Atezolizumab treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Inhaled steroids are allowed for management of asthma, and dermatological formulations are allowed to reduce the intensity of injection site reactions.
- Medications or vaccinations specifically prohibited in the Exclusion Criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation of trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor's Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's trial therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject.

Subjects who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

7 SAFETY AND PHARMACOVIGILANCE

7.1 Adverse Event (AE)

An AE is defined in ICH E6 as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it fulfills one or more of the following:

- Results in subject's withdrawal by the Investigator
- Is associated with an SAE
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance
- A new condition or the worsening of a pre-existing condition will be considered an AE.
- AEs do not include the following:
- Medical/surgical procedures are not AEs (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE if the procedure was not planned at screening visit.
- Overdose of concomitant medication without any signs or symptoms unless the subject is hospitalized for observation.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Disease progression

All AEs, whether observed by the Investigator or designee or volunteered by or elicited from the subject, should be recorded individually on an AE CRF page with the following information: the specific event or condition, whether the event was present pre-baseline or not, the dates and times (using the 24 hour clock, where midnight is 00:00 and noon is 12:00) of occurrence, duration, severity, relationship to study medication, action taken to study drug, outcome, and whether considered non-serious or serious, drug-related or not.

Once the subject has signed the Informed Consent Form (ICF), AEs will be recorded until the end of the Follow-up period. The severity of the AE will be assessed by the investigating physician in accordance with the definitions below. A Serious AE must fulfill the requirements listed in Section 7.2.

Adverse Event severity (Table 2) will be recorded and graded according to the latest version of the NCI-CTCAE (currently version 4.03) and coded into the database according to the latest version of MedDRA (currently version 19.0).

Table 2 Severity of Adverse Events According to CTCAE (Version 4.03)

Grade	Description
0	No AE or within normal limits
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.
A single dash (-) indicates a grade is not available

The following definitions should be used for toxicities/AEs that are not defined in the CTCAE:

- Mild (Grade 1): The AE is noticeable to the subject but does not interfere with routine activity, no medical intervention is required;
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest;
- Severe (Grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy;
- Life-threatening (Grade 4): The subject is at immediate risk of death.

The Investigator will document his opinion of the relationship of the AE to treatment with investigational product using the criteria outlined in Table 3.

Outcome to Date are classified as follows:

- Recovered: The subject has fully recovered from the AE with no residual effects observable
- Recovered with sequelae: The subject has recovered from the AE with residual effects observable
- Improved: the subject status improved but has not been fully recovered

- Ongoing: AE is not recovered
- Fatal
- Unknown

AEs will be coded by Data Management using the latest version of MedDRA (currently version 19.0) AE dictionary.

All AEs, serious and not serious, will be recorded on the AE Case Report Form, and if relevant, the Concomitant Medications Record in the CRF will be updated. Severity and relationship to study drug will be assessed by the Investigator as described in Table 3. Particular attention should be made to ensure no discrepancies between the AE and the SAE form (i.e. outcome, severity, relationship must be consistent).

Treatment emergent AEs (TEAEs) are defined as AEs observed after 1st dose of study drug.

Table 3 Relationship of Adverse Event to Treatment

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

7.2 Serious Adverse Events (SAEs)

An SAE is any AE occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational medicinal product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- a persistent or significant disability/incapacity
- a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

Hospitalization for elective treatment of a pre-study condition (pre-baseline) that did not worsen while on study and optional hospitalizations not associated with a clinical AE (e.g. elective cosmetic surgery) are not considered SAEs.

Significant medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; such an AE will normally be considered serious by this criterion.

A **life-threatening** adverse drug experience is any AE that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Any newly emergent SAEs, after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation, should be recorded and reported immediately to Sponsor or delegate.

7.3 Definition of an Unexpected Adverse Event

An **unexpected** adverse drug event is any AE, the specificity or severity of which is not consistent with information in the current Investigator's Brochure for an unapproved investigational product.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SAE assessed as unexpected by the Sponsor and that is judged by either the reporting Investigator or the Sponsor to have a reasonable causal relationship to the investigational medicinal product.

7.4 Exceptions in the Reporting of SAE

According to EU and FDA detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, regarding clinical trials in high morbidity or mortality diseases, it is acceptable to define some exceptions in the immediate reporting of specific SAEs. Refer to EU guidance ENTR/CT3,

5.1.9 and FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" (Dec 2012).

Elevation of blood cells is an expected event related to the mechanism of action.

These AEs will be thoroughly handled and followed up through the CRF (AE form) and will be reviewed monthly by the medical safety officer and could be re-qualified for reporting if necessary.

Each event must be carefully analyzed by the Investigator's designee to decide whether the SAE could be considered as an exception or must be immediately reported.

7.5 Notification of Serious Adverse Event (SAE)

7.5.1 Initial notification of SAEs

An Initial SAE report form must be completed and sent through the CRF **to the Medical Monitor** within 24 hours of the Investigator's knowledge of the event. **Any fatal or life-threatening event should be reported immediately, by phone, fax or email. Reporting SAEs to regulatory authorities and/or IRBs will comply with local regulations.**

Medical Monitor: [redacted]
E-mail: (for SAE related correspondences only): [redacted]
Fax: [redacted]

The Initial SAE report will be followed within 24 hours by a completed SAE report including a sufficiently detailed narrative to allow for a medical assessment of the case, as well as copies of hospital case reports, results of applicable diagnostic tests, laboratory results, biopsy results, autopsy reports and other documents when requested and applicable.

Minimum criteria for a valid initial SAE case

For regulatory purposes, initial SAE reports should be submitted to Medical Monitor and/or the Sponsor immediately and should include:

- A suspected investigational medicinal product,
- An identifiable subject (e.g. study subject code number),
- An AE with the Investigator's assessment of seriousness and relationship to study drug,
- An identifiable reporting source (Investigator contact details).

Once sent, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's site file.

In addition, all SUSARs and relevant SAEs will be reported to the IRB/IEC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

7.5.2 Follow-up of SAEs

Follow-up of all SAEs that occur during the study will continue until their satisfactory resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" if mutually agreed by the Investigator and Sponsor.

A Follow-up SAE Report Form must be completed by the site (marked as "Follow-up report") and sent to the Medical Monitor within a reasonable timeframe (an SAE Follow-up report is required whether or not there is any additional information to the initial report).

The contact information for Follow-up SAE reporting is the same as for initial SAE reports (see above section).

As for the initial SAE report, once sent, the Follow-up SAE report and accompanying documentation should be placed in the SAE section of the Investigator's site file.

7.6 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded 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 7.5). No safety data related to overdosing of Atezolizumab or BL-8040 are available.

7.7 Guidelines for Management of Patients Who Experience Specific Adverse Events while being treated by Atezolizumab + BL-8040

Guidelines for the management of patients who experience specific adverse events are provided in the Atezolizumab Investigator's Brochure, Appendix I and are outlined below:

- The Atezolizumab Investigator's Brochure and Appendix I provides guidelines for the management of patients who experience Atezolizumab-associated IRRs and immune-related pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic, and meningoencephalitis events. It is recommended that Atezolizumab be withheld or discontinued per the guidelines in the Atezolizumab Investigator's Brochure and that BL-8040 be withheld or discontinued per the guidelines in this section.

- For cases in which management guidelines are not covered in this section, Appendix I or the Atezolizumab Investigator's Brochure, patients should be managed, and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Event	Action to Be Taken
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in the Atezolizumab Investigator's Brochure for Atezolizumab. • For anaphylaxis precautions, see Appendix F. • For severe hypersensitivity reactions, permanently discontinue Atezolizumab and BL-8040.
Injection-site reactions	• Clinically appropriate measures (according to institutional guidelines) should be considered in case of BL-8040–related local reactions at the injection site (e.g., local treatments with steroids and or antihistamines) or systemic reactions (e.g., systemic antihistamines and steroids) or for preventive treatment before subsequent doses.
Overdose of BL-8040 (dose ≥ 3.75 mg/kg)	• Observe patient for any signs of toxicity and provide appropriate supportive treatment as indicated. • Patients with low blood counts should have blood counts monitored until recovery.
Pulmonary events	

Event	Action to Be Taken
Pulmonary event, Grade 1	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue BL-8040. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold BL-8040. • Monitor WBC count. • If event resolves to Grade 1 or better and WBC count is $\leq 60 \times 10^9$/L (60,000/μL) within 21 days, resume BL-8040. If not, permanently discontinue BL-8040. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Permanently discontinue BL-8040.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue BL-8040.
Diarrhea or colitis, Grade 2 or 3	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold BL-8040. • If event resolves to Grade 1 or better within 21 days, resume BL-8040. If not, permanently discontinue BL-8040.
Diarrhea or colitis, Grade 4	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Permanently discontinue BL-8040.
Dermatologic toxicity	
Rash, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue BL-8040.
Rash, Grade 3	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold BL-8040. • If event resolves to Grade 1 or better within 21 days, resume BL-8040. If not, permanently discontinue BL-8040.
Rash, Grade 4	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Permanently discontinue BL-8040.
Leukostasis	

Event	Action to Be Taken
Clinical evidence of leukostasis or WBC count > 60 × 10^9/L (60,000/μL)	• Withhold BL-8040 and Atezolizumab. • Consider leukapheresis. • At the discretion of the investigator and according to each site's institutional guidelines the patients may be treated with chemotherapy, leukapheresis, hydroxyurea or any other treatment accepted at the specific site. • Monitor patients with shortness of breath and administer oxygen to patients with reduced oxygen saturation. • Monitor WBC count daily. • If WBC count improves to ≤ 60 × 10^9/L (60,000/μL) and there are no signs of leukostasis within 21 days, resume BL-8040. If not, permanently discontinue BL-8040. • Monitor WBC count prior to dosing at least until WBC count has recovered to ≥ 40 × 10^9/L (40,000/μL).
BL-8040–related toxicities not described above	
Grade 3	• Withhold BL-8040. Continue Atezolizumab. • If event resolves to Grade 2 within 21 days and Medical Monitor agrees that BL-8040 should be continued, resume BL-8040 with a different schedule of SC injections. If not, permanently discontinue BL-8040. • If event resolves to Grade 1 or better within 21 days, resume BL-8040. If not, permanently discontinue BL-8040.
BL-8040–related toxicities not described above	
Grade 4	• Withhold BL-8040 and Atezolizumab. • If event resolves to Grade 2 or better within 21 days and Medical Monitor agrees that BL-8040 should be continued, resume BL-8040 with a different schedule of SC injections. If not, permanently discontinue BL-8040. • If event improves and Medical Monitor agrees that Atezolizumab should be continued, resume Atezolizumab. If not, permanently discontinue Atezolizumab.
Atezolizumab-related toxicities not described above	
Grade 3	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold BL-8040. • If event resolves to Grade 2 within 21 days and Medical Monitor agrees that BL-8040 should be continued, resume BL-8040 with a different schedule of SC injections. If not, permanently discontinue BL-8040. • If event resolves to Grade 1 or better within 21 days, resume BL-8040. If not, permanently discontinue BL-8040.

Event	Action to Be Taken
Grade 4	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold BL-8040. • If event resolves to Grade 2 or better within 21 days and Medical Monitor agrees that BL-8040 should be continued, resume BL-8040 with a different schedule of SC injections. If not, permanently discontinue BL-8040.

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin

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

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

7.8 Injection-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment injection should be captured as a diagnosis (e.g., "injection-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 Injection-Related Reaction eCRF. Separation should be made between “injection site reaction” and “systemic reaction”. 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 Injection-Related Reaction eCRF.

8 STATISTICAL METHODOLOGY

This section describes the statistical methods that will be used to analyze data from the BATTLE study. A more detailed SAP will be developed following the recruitment of the 20th subject and the receipt of study database. Should the methods of the SAP differ from the methods in this section, the methods of the SAP will prevail.

8.1 Analysis Sets

- Intention-To-Treat (ITT) Analysis Set: All enrolled subjects.
- Modified Intention-To-Treat (mITT) Analysis Set: Enrolled subjects who were treated at least once with both BL-8040 and with Atezolizumab.

8.2 Sample Size Justification

The planned sample size of 60 subjects is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of the proposed combination therapy in subjects with Acute Myeloid Leukemia.

8.3 Significance Level and Multiplicity Adjustment

The overall alpha level for this study is [redacted]. Confidence interval will be calculated for the efficacy endpoint in order to potentially explore the effectiveness of the proposed combination therapy: 1-sided 95% VI's for survival analysis derived metrics and 2-sided 95% CI's for change from baseline.

8.4 Efficacy Endpoints and Analyses

All efficacy endpoints are secondary and exploratory endpoints.

8.4.1 Relapse Free Survival as a Secondary Endpoint

The time from CR to occurrence of earlier relapse or death from any cause (RFS). In case of death following relapse, the relapse will be considered as study event. Subjects who were lost to follow-up for whatever reason and the attempt to obtain missing data on deaths/relapses failed will be right censored at the time of early study discontinuation.

This endpoint will be presented using a Kaplan-Meier plot and a 1-sided lower 95% CI for the observed median time to event [[redacted]] will be calculated.

Any estimate quoted from the Kaplan-Meier plot will have the estimate and the standard error (SE) of the estimate provided. Greenwood's formula will be used to calculate the SE.

8.4.2 Changes in MRD status, measured from baseline to Cycles 3, 9, 18 and 34 using quantitative multi-color flow cytometry

A repeated measures model ([redacted]) including the categorical month in trial and baseline MRD status as one degree of freedom covariate and an unstructured covariance matrix for repeated observations within subjects will be used.

To drive the Least Square Means (LSM) of the changes from baseline to each time point and two-sided 95% confidence interval.

8.4.3 Overall Survival (OS), measured as time from 1st study drug administration to death from any cause

Subjects not known to have died at last follow-up will be right-censored on the date they were last known to be alive.

This endpoint will be presented using a Kaplan-Meier plot and a 1-sided lower 95% CI for the observed median to event [[redacted]] will be calculated.

Any estimate quoted from the Kaplan-Meier plot will have the estimate and the standard error (SE) of the estimate provided. Greenwood's formula will be used to calculate the SE.

8.4.4 Event Free Survival (EFS), measured as the earlier from 1st study drug administration to the date of primary refractory disease, or relapse from CR, or death from any cause from 1st study drug administration

Subjects not known to have any of these events will be right-censored on the date they were last examined.

This endpoint will be presented using a Kaplan-Meier plot and a 1-sided lower 95% CI for the observed median time to event [[redacted]] will be calculated.

Any estimate quoted from the Kaplan-Meier plot will have the estimate and the standard error (SE) of the estimate provided. Greenwood's formula will be used to calculate the SE.

8.5 Safety and Tolerability Analyses

All safety assessments will use the ITT and mITT analyses sets.

8.5.1 Adverse Events

Adverse events will be recorded from the time a subject has signed the Informed Consent Form. The MedDRA dictionary will be used to standardize the terms used by the investigator to describe the Adverse Events (AEs). Adverse events analyses will include only the Treatment Emergent Adverse Events (TEAEs), namely, those events which started at the time of first study IP administration or afterwards.

The following analyses are pre-planned for adverse events:

- The incidence (no. of patients) and frequency (no. of events) of most frequent TEAEs (>5%) by Preferred Term (PT).
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by System Organ Class (SOC) and PT.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by SOC, High Level Term (HLT) and PT.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs by SOC and PT in Subjects Early Discontinued from Study/Treatment.
- The incidence (no. of patients) and frequency (no. of events) of serious TEAEs by SOC and PT.
- The incidence (no. of patients) and frequency (no. of events) of serious TEAEs by SOC, HLT and PT.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by severity.
- The incidence (no. of patients) and frequency (no. of events) of injection site reactions TEAEs.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs broken down by relationship to study IMP.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by action taken with study IMP.
- The incidence (no. of patients) and frequency (no. of events) of TEAEs when broken down by event outcome.

Adverse Events dictionary used to code Investigator's verbatim terms will be provided.
Individual subject listings of all SAEs, treatment emergent SAEs, TEAEs and non-TEAEs.

8.5.2 Dose-Limiting-Toxicity Assessment

Dose-limiting toxicity (DLT) is defined as a clinically significant adverse event (AE) or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness or concomitant medications and occurring during the first treatment cycle that meets any of the following criteria (refer to Table 2 for CTCAE severity grading):

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) or bilirubin for ≥ 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant, non-hematological NCI common terminology criteria that are CTCAE grade 3 or 4
- Change from baseline to Grade 4 neutropenia or thrombocytopenia lasting for >4 weeks in the absence of persistent Leukemia.
- Symptomatic leukostasis

To be considered a DLT the toxicity must be possibly, probably or definitely related to either of the study drugs or the combination.

An AE must be clinically significant to define DLT, e.g., nausea and vomiting, alopecia, study drug-related fever or electrolyte abnormalities that are ≤ grade 3 will not constitute DLT. For subjects who experience a DLT, the study continuation should be discussed with the Medical Monitor. Subjects who experience AEs that are not considered DLT or are unrelated to BL-8040 or Atezolizumab may continue study participation at the discretion of the Investigator.

BL-8040 injections may be skipped for any reason as per Investigator judgment; however, they must be skipped in the case of a WBC >60,000/μL, measured prior to administration of the next BL-8040 injection and/or evidence of leukostasis.

Increase in WBCs will not be considered as a DLT since is a direct effect of CXCR4 inhibition and reflects the drug's mechanism of action.

In case of elevated WBC > 60,000/μL, daily WBC assessment should be done, and BL-8040 treatment can be resumed provided that the WBC counts decrease to ≤ 60,000/μL. Pre-dosing WBC monitoring should continue as long as the WBC count is ≥40,000/μL. For values <40,000/μL daily WBC monitoring may be stopped and further analysis should be done based on the Investigator's judgment.

Safety review of the accumulated data will be performed by an independent DMC after the first 6 subjects have completed the first cycle of combination therapy and again after 6 additional subjects have completed the first cycle of combination therapy. The number of active subjects in the DLT assessment period will not exceed the potential for observing that the combination would be considered unacceptably toxic according to the criteria above. The DMC will evaluate the safety data of the first 6 subjects and further after the first 12 subjects if needed. In case 5 out of the 6 of the first patients do not experience a DLT the recruitment will not stop (as two DLT in the first 6 patients will not have been reached) and the DMC will review the safety data without stopping recruitment. In case of expansion of the Safety DLT Cohort to 12 patients, the same rules will apply. In case we have > 1 DLT out of 5 patients (or >3 out of 11), they study recruitment will stop for DMC assessment and recommendations before study continuation. In order to be evaluable for the DLT assessment period, a subject must complete the first cycle of treatment. If a subject is discontinued before completion of the first cycle (unless due to a DLT), an additional subject will be recruited and included in the Safety DLT Cohort to ensure a total of six evaluable subjects. Similar rules will be applied in case the Safety DLT Cohort is expanded to 12 subjects. The subjects that are discontinued early will be included in all the other relevant analyses according to the population described in the statistical analysis section.

DMC recommendations will thereafter be presented to the Sponsor. The guidelines to be used by the DMC for the review of the Safety DLT Cohort are presented below:

- If ≤1 out of 6 subjects experience a DLT during the first cycle of treatment, the combination treatment will be considered as eligible for further evaluation and recruitment will continue without a pause.
- If ≥ 2 out of 6 subjects experience a DLT, the DMC will assess the risk/benefit profile of the combination treatment and recommend one or more of the following: 1) Safety DLT Cohort should be expanded to 12 subjects, 2) the protocol should be modified, 3) the treatment schedule should be changed, or 4) the study should be discontinued.
- If ≤ 2 out of 12 subjects experience a DLT in the expanded Safety DLT Cohort, recruitment will continue to the full proposed study size.
- If >2 out of 12 subjects experience a DLT in the expanded Safety DLT Cohort, the DMC will determine whether recruitment will be stopped, or recruitment can be continued with or without a protocol modification.

8.5.3 Safety Laboratory Data

Analyses of safety central laboratory data will be performed in the following manner:

- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. The incidence (no. of subjects) of abnormal values at any time post initiation of the 1st study IMP administration, calculated for subjects with normal values at baseline will be provided. Analysis will include, per tested parameter, those subjects with normal baseline and at least one post-treatment measurement. Summary table will display the number and relative percentage of subjects with at least one abnormal value (above upper or below the lower normal range) at any time post initiation of the 1st study IMP administration.
- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. Shift analysis of the categorical change from baseline to each scheduled visit and to the last observed value will be provided.
- Box-Plots of measurements done and figures of mean values ±SEs as well as descriptive statistics for all laboratory quantitative parameters and changes from baseline will be provided by scheduled visits.

8.5.4 Vital Signs

Analyses of vital signs data will be performed in the following manner:

- The more detailed SAP will provide the quantitative criteria used to define the potentially clinically significant (PCS) abnormal vital signs values. Measurements to be used in the analysis are those taken immediately following the first administration of the study IMP and onwards. The incidence tables of PCS values as well as the individual subject listing will be provided. The denominator to be used for calculating percentages is the number of subjects with at least one observation post 1st study IMP administration.
- Box-Plots of measurements done, figures of mean values ±SEs as well as descriptive statistics for all parameters and changes from baseline (derived) will be provided by scheduled visits and treatment groups.

8.5.5 Physical Examinations

Analyses of physical examinations will be performed in the following manner:

- Distribution of number of subjects by body system examined and result assessments made will be presented at baseline and at termination.
- Shift analysis of categorical change by body system will also be performed.
- Incidence and listings of individual subject's findings of Abnormal Clinically Significant following 1st study IMP administration and onwards will also be provided.

8.5.6 12-Lead ECG

12-lead ECG will be recorded on Days 1 and 2 of treatment cycle 1 at pre-dose and 4 ± 2 h post-BL-8040 administration. Additional ECGs may be performed at the discretion of the Investigator. Analyses of ECG evaluations are presented in the report in the following manner:

- Descriptive statistics and Box-Plots of quantitative 12-Lead ECG parameters measured by scheduled timepoints (Pre-Dose/Post-Dose) as well as their changes from baseline.
- Distribution of the number of subjects by the interpretation (Normal/Abnormal) at each scheduled timepoint.

- Listing of QTC Interval Fridericia (msec) Measurements > 450 msec AND changes from baseline > 60 msec will be listed along with baseline value and change from baseline.

8.5.7 Tolerability Assessment

Tolerability and drop-out assessments will be performed for the ITT and mITT analyses sets.

Tolerability analysis will be based on the number and percent (%) of subjects who failed to complete the study IMP dosing period and will be presented by withdrawal reason.

The time to withdrawal will be presented using a Kaplan-Meier Plots. Any estimate quoted from these plots will have the estimate and the standard error (SE) of the estimate provided. Greenwood's formula will be used to calculate the SE.

8.6 Exploratory Outcome Measures

- Biomarkers that may serve as surrogates or predictors of clinical efficacy (PD-L1 expression, CXCR4 expression, and presence of immune cells).
- Immune response to BL-8040 and Atezolizumab.
- Presence of ADAs during the study relative to the presence of ADAs at baseline.
- Pharmacodynamic endpoints.
- Measurement of mast cell activation
- Molecular tests may be assessed following emerging public domain literature and other clinical trials with BL-8040.

Univariate statistics will be presented using Box Plots. Any analysis adjustments to the data analysis will be accomplished using Mixed Model Analysis of Variance. Significant findings in the model will be presented by providing the estimate and its calculated SE.

8.7 Pharmacokinetics (PK) Assessment

Sparse samples will be collected for PK analysis and to compare exposure in this study with that attained in previous studies. Serum concentrations of Atezolizumab and plasma concentrations of BL-8040 will be reported as individual values and summarized (mean, SD, coefficient of variation [%CV], median, range, geometric mean, and geometric mean CV [%CV]) by cycle, when appropriate and as data allow. Atezolizumab or BL-8040 concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution and AUC, as warranted by the data.

8.8 Statistical Analysis Plan (SAP)

A detailed SAP will be developed following the recruitment of the 40th subject.

Any deviation from this Statistical Analysis Plan (SAP) will be reported in the Clinical Study Report.

8.9 Statistical Analysis Software

All data listings, summary tables and statistical analyses will be generated using SAS® Version 9.4 or higher (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA).

9 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

Prior to initiation of the study, the Investigator will submit the study protocol and amendments, Investigator's Brochure and amendments, ICF and any other documents that may be provided to the subject or any other documents requested by the IRB/IEC for review and approval.

The names and affiliations of all members of the IRB/IEC must be provided to the Principal Investigator and BioLineRx. In lieu of this, the IRB/IEC must certify that it has been officially authorized/recognized according to the national legislation.

The IRB/IEC must provide written approval of the study to keep in the Investigator's file. Records of approval of all documents pertaining to this study, including the local regulatory authority, should be filed as such. The Investigator will not begin the study until the protocol, ICF and any other document provided to the subject have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening conditions or death. The IRB/IEC will also be notified of Part 1 preliminary results.

9.2 Ethical Conduct of the study

All clinical work conducted under this protocol is subject to ICH GCP (E6) guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with Sponsor and/or designee's standards operating procedures and the following guidelines:

GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).

Declaration of Helsinki: Seoul, 2008.

US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312) and/or EU Directives; and/or local country regulations and guidelines.

9.3 Subject Information and Consent

Prior to screening for the study each subject will be informed in detail about the study drugs to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved ICF prior to the conduct of any study-related activity. A copy of the ICF will be submitted together with this protocol and must be approved by the IRB/IEC prior to study commencement. Each subject will be given a copy of the written ICF, and each subject's chart will include the signed ICF for study participation. The original subject signed and dated ICFs will be maintained per ICH record retention requirements. The consent form will also be signed by the person administering the informed consent. An entry should be made in the subject's dated source documents to confirm that the informed consent was obtained prior to administering any study related procedures. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or

by the subject's legally acceptable representative's dated signature. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having performed so during the study.

9.4 Subject Insurance

A product liability to cover against injury and damages arising from the use of investigational products in this project is provided by the Sponsor for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the Investigator's site file or can be made available to the Investigator and to the IRB/IEC upon request.

Subjects will be insured through contract between an insurance company and the Sponsor.

9.5 Informing the General Practitioner

When required by location regulation, the Investigator will inform the subject's primary care physician of his/her participation in the study, by sending a letter to the physician.

9.6 Personal Data Protection

The Sponsor will comply with local regulations and with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all subject data will be identified only by a subject identification number and subject initials and date of birth. The data will be blinded in all data analyses. The subject must be informed and consent to authorized personnel of the Sponsor, such as study monitor, auditor, etc. and relevant health regulatory agencies having direct access to personal medical data to assure a high-quality standard of the study. At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

9.7 Data and Safety Monitoring

A DMC will be assigned by the Sponsor prior to the beginning of the study. The committee will be comprised of 3 members appointed by the Sponsor including at least one clinician and persons knowledgeable of the investigational drug.

After treatment of 6 patients, the DMC will review the safety data to assess the progress of the clinical trial and will recommend to the Sponsor and to the Investigator whether to continue with the current combination, expand the DLT period revision to assess 12 patients, modify the dose regimen or stop the trial. In case 5 out of the 6 of the first patients do not experience a DLT the recruitment will not stop (as two DLT in the first 6 patients will not have been reached) and the DMC will review the safety data without stopping recruitment. DMC activities and procedures will be described in detail within the DMC charter.

9.8 Protocol Exceptions and Deviations

Departures from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations, and if possible the reason for occurrence, will be documented by the study monitor for visit reports and will be included in the final clinical study report. The Investigator must report any protocol deviations to the Sponsor or the Sponsor's designee, should they occur. If required, the Investigator should also report deviations to the IRB/IEC in accordance with local regulations and within a reasonable time. No prospective waivers will be allowed for patients who do not fulfill the inclusion/exclusion criteria.

9.9 Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/IEC in accordance with local requirements and, if required, to the Regulatory Authority, either as an amendment or a notification. Approval for amendments must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval is required for notifications.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted according to GCP as outlined by ICH Topic E6 step 5 guidelines. The CRO's SOPs will be followed to ensure that clinical trials are conducted, and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

10.1 Audits and Inspections

The study may be audited according to the Sponsor's or its designee's QA inspection program. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the study protocol and ICH GCP guidelines. Audit visit(s) will be arranged in advance with site personnel at a mutually acceptable time.

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its designees or the regulatory authority inspectors after appropriate notification. The verification of the CRF data must be made by direct inspection of source documents. The auditor may ask to visit the facilities where laboratory samples are collected, where the investigational product is stored and prepared and any other facility used during the study. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 Study Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements.

Before study initiation, at the site initiation visit or at an Investigator's meeting, a Sponsor or CRO representative will review the protocol and CRFs with the Investigator and his staff. The Sponsor/CRO will also be responsible for training study personnel in the study specific procedures.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator and his staff. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and accuracy with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and will periodically review the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g., local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a

mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to enquiries.

The Investigator will ensure that the study participants are aware of and consent to their personal information being scrutinized during the data verification process, as part of study-related monitoring, inspection and/or auditing, by properly authorized persons associated with Sponsor or by domestic and/or foreign regulatory authorities. However, the subject's participation and personal information will be treated as strictly confidential to the extent that the applicable law permits and will not be made publicly available.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The details of the monitoring procedures are listed in the study-specific Monitoring Plan.

10.3 Quality Laboratory Standards

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central and local institution laboratories.

Before the study begins, the laboratories to be used in the study will provide a list of the reference ranges for all laboratory tests to be undertaken and details of the method used for quality control. These will be held in the Investigator Site File and the Trial Master File. The methods employed for each assay should be available on request. Any change in the laboratory, its procedures, references, values, etc. during the study must be notified promptly to the Sponsor.

11 STUDY DOCUMENTATION

Study documents will include the following:

Signed ICFs

Source documents (e.g. subject files, medical notes)

Investigator copies of the CRFs and SAE reports

Investigator site file + contents

Study manual (if applicable)

Study Pharmacy manual (includes instructions for use)

Investigator meeting binder, laboratory manuals and/or other training materials

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

11.1 Source Documents

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/IEC review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records or completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc etc.). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for subjects registered to the study should indicate the date the ICF was signed, participation in a clinical trial with the clinical protocol number and title, treatment number and evidence that inclusion/exclusion criteria have been met.

11.2 Recording of Data on Case Report Form (CRF)

The development of the CRF will be the responsibility of the Sponsor or its designee.

All eCRFs will be completed in English and will be reviewed by study monitors for accuracy and completeness. All data pertaining to the visit should be recorded in the eCRF no later than five days after the completion of the visit. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct. The PI must sign the completed CRF prior to its submission to the Sponsor.

A representative of the Sponsor or designee will instruct the Investigator and his/her staff prior to the enrollment of the first patient and will train them on recording the findings into the electronic data capture (EDC) system.

After the enrollment of the first patient, a study monitor will periodically monitor the progress of the study by conducting onsite visits. The study monitor will also have the ability to review query statuses remotely which may warrant more frequent contact with the Investigator and his/her staff. The Investigator will make available to the study monitor the computer that accesses the eCRFs, source documents, signed consent forms and all other study related documents. The Investigator will be responsible for reviewing eCRFs, providing resolution to data queries generated by the study monitor via the EDC system, providing missing or corrected data, and approving all changes performed on his/her data, and endorsing the patient

data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password, that together would represent a traditional handwritten signature.

The Investigator will agree to the inspection of study-related records by the Sponsor, external auditor and/or health authority representatives.

11.3 Investigator Site File

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor/or designee and regulatory agencies.

12 CLINICAL TRIAL SUPPLIES

The Sponsor or designee will be responsible for supplying clinical trial supplies to the sites. The Principal Investigator will be responsible for the administration, inventory and accountability of all clinical trial supplies provided to the site, exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will return the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. A copy of these records should be maintained in the site study files. **Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol.**

13 DATA MANAGEMENT

Data Management services will be provided by the Sponsor or designee. The data management system will be specified in the Data Management Plan.

After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity and validity of the database. These edit checks may include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

Adverse events will be coded using the latest version of MedDRA (currently version 19.0). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

14 STUDY ADMINISTRATION

14.1 Participating Centers

Centers in the USA-5 sites , Europe-15 sites and Israel-2 sites. Optional centers can be opened in other countries..

14.2 Required Documents Prior to Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

Appropriate local health authority documentation properly signed and dated by the required Investigator (i.e., documents required for submission to the local IRB/IECs or applicable regulatory authorities).

Signed copy (original) of the approved protocol

Acknowledgement of receipt of the approved Investigator Brochure

Completed and signed statement of Investigator

A signed Clinical Trial Agreement

Curriculum vitae for the Investigator and sub-Investigator (can be collected at site initiation visit)

Financial Disclosure Forms for the Principal Investigator and Sub-Investigators

IRB/IEC name and address; and membership list (can be collected at site initiation visit)

Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and ICF (identified by protocol title and number)

Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor)

Provisions for direct access to source/data documents, if necessary, for trial-related monitoring, audits, IRB/IEC review and regulatory inspection

Name and location of the laboratory utilized for laboratory assays and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at site initiation visit)

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, the Sponsor will arrange for study drugs to be delivered to the study site. Supply of all other study materials will be the responsibility of the Sponsor and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo study initiation to include review of study protocol, instructions for CRF completion, AE reporting and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will be provided with an Investigator's File. This file should be used for all trial related documents. The Investigator will be responsible for keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

14.3 Study Completion

This study is expected to end when all required subjects have been enrolled and the last subject has completed the study and all query resolutions have been completed.

Data and materials that are required before the study can be considered complete and/or terminated include, but are not limited to:

Laboratory findings, clinical data and all special test results from screening through the end of the follow-up period

CRF properly completed by appropriate study personnel and electronically signed by the Investigator

Completed Drug Accountability Records

Statement of outcome for each SAE reported

Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable)

Retention of Study Documents Statement

14.4 Clinical Study Report

A clinical study report will be developed by the Sponsor on completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

14.5 Retention of Study Records

The Investigator will retain copies of the approved protocol, completed CRF, signed ICFs, relevant source documents and all other supporting documentation related to the project as defined in ICH-E6 section 8 related to the project per ICH-E6 record retention requirements for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product in a secure and safe facility with limited access. If the Investigator is unable to retain the study documents for the required amount of time, the Sponsor or designee must be informed of the individual who will be assuming this responsibility.

The Sponsor will notify, in writing, the Investigator when the clinical study data may be discarded. The Investigator will take measures to prevent accidental or premature destruction of these documents.

These files must be made available for inspection upon reasonable request by authorized representatives of the Sponsor and/or the relevant regulatory agencies.

14.6 Confidentiality and Publication of Study Results

14.6.1 General

All data and information supplied by or on behalf of the Sponsor or otherwise acquired or obtained by any Research Institution, the Principal Investigator and other Investigators ("Recipients") in any manner, in connection with or in performance of this study, is considered "Confidential Information". This Confidential Information includes, but is not limited to, the Investigator’s brochure, this protocol and any information relating thereto, CRFs and other scientific data, information relating to Sponsor's Investigational Product and treatment methodology and information relating to Sponsor's (or its affiliates') commercial, technical and financial information, research technology, products, inventions, trade secrets and research and development. The results produced in performance of the study and any data, information or other material collected, developed, generated or prepared during and in the course of performing the study shall be promptly disclosed to Sponsor in full in writing, and are also considered Confidential Information. This Confidential Information shall be and remain the sole property of the Sponsor. Except for Publishable Results (defined below) to the extent it may be published under Section 14.6.2, throughout the duration of the study and after its

completion, Recipients shall not disclose Confidential Information to others without the written consent of the Sponsor, except to those of its employees who have a need to know the Confidential Information in order to Recipients' obligations hereunder, and where such employees are bound by written contractual obligations covering Confidential Information that are no less restrictive or protective than those contained herein, provided that Recipients shall remain liable for any disclosure or use of Confidential Information by such employees, (ii) use the same degree of care to preserve confidentiality of Confidential Information as they use for their own information of like nature, which shall not be less than reasonable degree of care, and (iii) not use Confidential Information for any purpose except in the performance of this study. Promptly at Sponsor's request, or upon completion of the study, Recipients will discontinue use and return to Sponsor or destroy, in accordance with Sponsor's instructions, all copies or other manifestations of Confidential Information that may be in their possession or control, except to the extent expressly required hereunder and to comply with Applicable Laws (defined below). Should a Recipient be required to disclose Confidential Information pursuant to law, regulation, judicial or administrative order or request by a governmental or other entity authorized by law to make such request, Recipient shall (i) promptly notify Sponsor prior to such disclosure, (ii) cooperate with Sponsor and provide assistance in seeking a protective order or other suitable protection with respect to the Confidential Information, and (iii) only disclose such Confidential Information to the extent pursuant to said law, regulation, judicial or administrative order, or request by a governmental or other authorized entity.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The personal physician will be notified by site personnel of subject participation in the study.

14.6.2 Published Data

The object of the study will be to publish the results of the complete study ("Publishable Results") in an appropriate peer-reviewed journal after the conclusion of the study ("Publication"). A formal Publication of the Publishable Results is planned and will be considered a joint publication by the Principal Investigator, other Investigators, Sponsor and the appropriate Sponsor personnel (and Research Institutions) (*Subject to internal review)*. Publication must be undertaken in a responsible and ethical manner, taking into account relevant external standards regarding the manner and content of scientific, technical and medical publications and in subject to applicable laws, rules, regulations, policies and guidelines ("Applicable Laws"). Authorship will be determined by mutual agreement between Sponsor and Principal Investigator. Sponsor shall be mentioned in all Publications unless contrary instruction is given by Sponsor. Review and comment by Sponsor authorized personnel on draft abstracts and manuscripts for Publication or presentation is required prior to publication or presentation. Authors shall submit a copy of any abstracts, manuscripts or other material proposed for publication or presentation ("**Draft Publications**") to the Sponsor for its approval no fewer than sixty (60) days prior to the intended date of submission of such Draft Publications to any journal, publisher, and/or third party. The Sponsor has the right, at its discretion (a) to evaluate Draft Publications for accuracy and concurrence regarding data, evaluations, and conclusions, (b) to provide an opportunity for Sponsor to share with the Investigator(s) any new or unpublished information of which he or she may be unaware, (c) to ensure that no Confidential Information or other Sponsor proprietary information is being utilized and has been included, and (d) evaluate Draft Publications to determine if patent applications need to be filed on any information disclosed therein.

If the Sponsor determines that such Draft Publication contains Confidential Information or could otherwise be detrimental to Sponsor's intellectual property interest or have other adverse

effects on its business, and notifies Principal Investigator of its determination, the Principal Investigator, Research Institutions and other Investigators/authors shall remove such Confidential Information from the Draft Publication or at Sponsor's election, modify it to remove language that is detrimental to Sponsor's intellectual property or other interests, and refrain from submitting such Draft Publication to a journal, publisher and/or other third party for additional ninety (90) days from Sponsor's notification to allow for filing of patent applications or the taking of such other measures as Sponsor deems appropriate to establish, preserve and protect its intellectual property or other interests. Principal Investigator, other Investigators and Research Institutions further agree to redact or modify those sections of the draft Publication in which Sponsor in good faith determines falls within (a) to (d) above.

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16 APPENDICES

16.1 Appendix A Schedule of Assessments

Study Procedure / Study Day	Screening Period	Baseline	Treatment Period			End of Treatment / Early Discontinuation	Follow-up	
		Pre-dose Day 1 Treatment Cycle 1	21-day treatment cycles for up 2 years (a maximum of 34 cycles)				Safety Follow-up	Survival Follow-up
	Day -28 to Day -1		Day 1[1]	Day 2	Day 3		30 days post study drug[2]	Every 3 months (± 1 month)
Informed consent	X							
Inclusion/exclusion criteria	X	X[3]						
Demographic & medical history	X							
Physical examination[4]	X	X	X			X		
Weight	X	X	X[5]					
Vital signs[6]	X	X	X	X	X	X		
ECOG Performance Status	X	X	X[7]			X		
12-lead ECG[8]	X	X	X	X		X		
Hematology[9]	X	X	X	X	X	X		

[1] Day 1 of each treatment cycle will have a ± 3-day window.

[2] The safety follow-up period may be extended up to 90 days after the last dose of study drug for any SAEs considered reasonable possibly related to BL-8040 and/or Atezolizumab.

[3] Review inclusion/exclusion criteria to confirm eligibility.

[4] Full physical examination at screening and End of Treatment visit. Directed physical examination to be performed at baseline and pre-dose on Day 1 of every subsequent treatment cycle.

[5] Weight will be measured pre-dose on Day 1 of every treatment cycle to determine the correct dose of BL-8040.

[6] Vital signs will include blood pressure, pulse rate, oral temperature, O_2 saturation levels and respiration rate. To be performed on. Days 1, 2 and 3 at pre-dose and 4 ± 2 h post-BL-8040 administration during the first cycle. In the following cycles pre-dose and 4±2h post BL-8040 administration on day 1 only.

[7] ECOG performance status will be determined pre-dose on Day 1 of every cycle.

[8] 12-lead ECG will be recorded on Days 1 and 2 of treatment cycle 1 at pre-dose and 4 ± 2 h post-BL-8040 administration. Additional ECGs may be performed at the discretion of the Investigator.

[9] Haematology and differential counts will be performed before each dose of BL-8040 throughout the study. During treatment cycle 1, samples will also be collected at 4 ± 2 h post-BL-8040 administration on Days 1, 2 and 3.

Study Procedure / Study Day	Screening Period	Baseline	Treatment Period			End of Treatment / Early Discontinuation	Follow-up	
		Pre-dose Day 1 Treatment Cycle 1	21-day treatment cycles for up 2 years (a maximum of 34 cycles)				Safety Follow-up	Survival Follow-up
	Day -28 to Day -1		Day 1[1]	Day 2	Day 3		30 days post study drug[2]	Every 3 months (± 1 month)
Biochemistry[10]	X	X	X		X	X		
Thyroid Function Tests[11]	X		X			X		
Coagulation[10]	X		X			X		
HIV, HBV, HCV serology	X[17]							
CT scan chest (within 28 days prior to treatment)	X							
Bone Marrow (BM) biopsy	X[12]							
Bone Marrow (BM) aspirate including MRD assessment, biomarker assessments and DNA/RNA for correlative studies	X[13]				X[13]	X[13]		
Peripheral blood immune-phenotyping, biomarker assessments and DNA/ RNA for correlative studies	X[13]		X[13]			X[13]		
BL-8040 SC injections			X	X[14]	X			
Atezolizumab IV infusion				X[15]				

[10] Biochemistry samples will be collected pre-dose on Days 1 and 3 of each treatment cycle.

[11] Thyroid function tests and coagulation will be performed pre-dose on Day 1 of every other treatment cycle starting from treatment cycle 2.

[12] Screening BM biopsy and aspirate only to be performed after Sponsor approval of provisional enrolment package.

[13] Bone marrow aspirate samples to be collected during the screening and post-dose on Day 3 of treatment cycles 3, 9, 18 and end of cycle 34 (or EOT, whichever comes first). Sample will be used for immune-phenotyping, and to measure CXCR4, PD-1 and PD-L1 expression.

[14] BL-8040 to be administered 1h (± 30 min) after completion of Atezolizumab infusion.

[15] Atezolizumab IV infusion during treatment cycle 1 to be administered over 1 h. If well tolerated, subsequent infusions to be administered over 30 min.

Study Procedure / Study Day	Screening Period	Baseline	Treatment Period			End of Treatment / Early Discontinuation	Follow-up	
		Pre-dose Day 1 Treatment Cycle 1	21-day treatment cycles for up 2 years (a maximum of 34 cycles)				Safety Follow-up	Survival Follow-up
	Day -28 to Day -1		Day 1[1]	Day 2	Day 3		30 days post study drug[2]	Every 3 months (± 1 month)
BL-8040 PK sampling[16]		X	X	X			X	
Atezolizumab PK sampling[16]				X		X	X	
BL-8040 ADA and complement activation[16]		X		X		X	X	
Atezolizumab ADA and compliment activation[16]			X	X		X		
Tryptase[16]		X	X	X				
Adverse events		←	—	—	—	—	→	
Concomitant medications	X	←	—	—	—	—	→	
Anti-cancer therapy status						X	X	X
Relapse and survival status							X	X

[16] For detailed BL-8040 and Atezolizumab PK, ADA, compliment activation and Tryptase testing, see Appendix B. the testing has a window of +/- 2 min for sampling within 1 hour of injection and +/- 5 min for sampling after 1 hour

[17] HIV testing performed at screening unless prohibited by local regulations.

16.2 Appendix B: PK and ADA Assessment

Visit	Time	Sample
Cycle 1 Day 1	Prior to first BL-8040 dose	• BL-8040 PK (plasma) • BL-8040 ADA (serum) • BL-8040 CA (serum) • Tryptase (plasma)
	1-hour post- BL-8040 dose	• BL-8040 CA (serum) • Tryptase (plasma)
	Post BL-8040 dose Full Profile	• BL-8040 PK (plasma) FP
Cycle 1 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • BL-8040 PK (plasma) • Tryptase (plasma)
	30 (+/-10) minutes after Atezolizumab infusion	• Atezolizumab PK (serum)
Cycle 2 Day 1	Prior to BL-8040 dose	• BL-8040 ADA (serum) • Tryptase (plasma)
	1-hour post BL-8040 dose	• Tryptase (plasma)
Cycle 2 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA(serum) • Tryptase (plasma)
Cycle 3 Day 1	Prior to BL-8040 dose	• BL-8040 PK (serum) • BL-8040 ADA (serum) • BL-8040 CA (serum) • Tryptase (plasma)
Cycle 3 Day 1	1-hour post BL-8040 dose	• BL-8040 PK (plasma) FP • BL-8040 CA (serum) • Tryptase (plasma)
Cycle 3 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • BL-8040 PK (plasma) • Tryptase (plasma)
	30 (+/- 10) minutes after Atezolizumab infusion	• Atezolizumab PK (serum)
Cycle 4 Day 1	Prior to BL-8040 dose	• BL-8040 ADA (serum) • Tryptase (plasma)
Cycle 4 Day 1	1-hour post BL-8040 dose	• Tryptase (plasma)
Cycle 4 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tryptase (plasma)
Cycle 8 Day 1	Prior to BL-8040 dose	• BL-8040 PK (plasma) • BL-8040 ADA (serum) • BL-8040 CA (serum) • Tryptase (plasma)
Cycle 8 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • BL-8040 PK (plasma)

Visit	Time	Sample
Cycle 12 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Cycle 16 Day 1	Prior to BL-8040 dose	• BL-8040 ADA (serum) • Tryptase (plasma)
Cycle 16 Day 1	1-hour post BL-8040 dose	• Tryptase (plasma)
Cycle 16 Day 2	Prior to the atezo infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tryptase (plasma)
30 days after last dose study drug (end or discontinuation of treatment)	Anytime At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • BL-8040 PK (plasma) • BL-8040 ADA (serum)

ATA = anti-therapeutic antibody; PBMC = peripheral blood mononuclear cell; PK =pharmacokinetic; FP= Full Profile
PK Full Profile: 15 mins; 30 mins; 1 hr; 2 hrs; 4 hrs; 8 hrs)

16.3 Appendix C AML Diagnosis Criteria

AML diagnosis is based on WHO classification of myeloid neoplasm and acute.

Table 1. WHO classification of myeloid neoplasms and acute leukemia

WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition

Table 1. (continued)

WHO myeloid neoplasm and acute leukemia classification
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

16.4 Appendix D Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]	
Description	**Grade**
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

[1] Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man*. Journal of Chronic Diseases, 11:7-33, 1960.

[2] Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol (CCT) 5: 649-655, 1982

16.5 Appendix E Preexisting Autoimmune Diseases

Patients should be carefully questioned with regard to 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 will be excluded from participation 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 with regard to any uncertainty over autoimmune exclusions.

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

16.6 Appendix F Anaphylaxis Precautions

EQUIPMENT NEEDED:
• Tourniquet
• 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 drug infusion, the following procedures should be performed:
1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
Continue to observe the patient and document observations. Use of a tourniquet is not applicable for patients receiving IV infusion via a central line.

16.7 Appendix G Response criteria in acute myeloid leukemia

Response criteria in acute myeloid leukemia

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD-})	If studied pre-treatment, CR with negativity for a genetic marker by real-time quantitative polymerase chain reaction (RT-qPCR), or CR with negativity by multi-color flow cytometry	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1,000/µL); platelet count ≥100 x 10^9/L (100,000/µL)	MRD positive or unknown
• CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/µL)] or thrombocytopenia [<100 x 10^9/L (100,000/µL)]	
• Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; 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 (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
• Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
• Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an 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 should last at least 3 months
• Progressive disease (PD)[a,b]	Evidence for an increase in bone marrow blast percentage 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 absolute neutrophil count (ANC) to an absolute level [>0.5 x 10^9/L (500/µL), and/or platelet count to >50 x 10^9/L (50,000/µL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25,000/µl) (in the absence of differentiation syndrome)[b]; or • New extramedullary disease	Category mainly applies for older patient given low intensity or single agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
• Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
• Molecular relapse (after CR_{MRD-})	If studied pre-treatment, reoccurrence of MRD as assessed by quantitative RT-qPCR or by multi-color flow cytometry	Test applied, sensitivity of the assay, and cut-off values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, i.e., 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.

16.8 Appendix H Outcome measures for clinical trials in acute myeloid leukemia

Category	Definition
Overall survival	Defined for all patients of a trial; measured from the date of entry into a clinical trial or from the date of diagnosis (e.g., for correlative science studies) to the date of death from any cause; patients not known to have died at last follow-up are censored on the date they were last known to be alive
Relapse-free survival (RFS)[a,b]	Defined only for patients achieving complete remission (CR), or CR with incomplete hematologic recovery (CR_i); measured from the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined
Event-free survival (EFS)[b]	Defined for all patients of a trial; measured from the date of entry into a study to the date of primary refractory disease, or relapse from CR, or CR_i, or death from any cause; patients not known to have any of these events are censored on the date they were last examined
Cumulative incidence of relapse (CIR)[b,c]	Defined for all patients achieving CR, CR_i; measured from the date of achievement of a remission until the date of relapse; patients not known to have relapsed are censored on the date they were last examined; patients who died without relapse are counted as a competing cause of failure

[a] Relapse-free and disease-free survival have been used with the same definition.

[b] In clinical trials in which the response criterion CR without minimal residual disease (CR_{MRD-}) is used, consideration should be given to include molecular relapse as assessed by quantitative polymerase chain reaction (RT-qPCR) or multi-color flow cytometry as a criterion for relapse; similarly, for analysis of EFS, no achievement of CR_{MRD-} may be regarded as an event. The definitions of RFS, EFS, and CIR must be clearly defined within each protocol.

[c] It is important to provide estimates of cumulative incidence of death (CID) as well, since just considering the results of CIR may be misleading if for instance CIR is lower for one group but CID is actually higher for that same group.

16.9 Appendix I Management of Atezolizumab Therapy Further to Adverse Events

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 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 4.

Table 4 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 1-2 mg/kg/day oral prednisone or equivalent. • 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 1-2 mg/kg/day oral prednisone or equivalent. • 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; IVIG = intravenous immunoglobulin

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

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

[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Hepatic Events

Immune-related hepatitis has been associated with the administration of Atezolizumab. 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 5.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have 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 5 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue Atezolizumab. • Monitor LFTs until values resolve to within normal limits.
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 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • 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.

LFTs = liver function tests.

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

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

[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Gastrointestinal Events

Immune-related colitis has been associated with the administration of Atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 6.

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 CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 6 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 1-2 mg/kg/day oral prednisone or equivalent. • 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 gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent 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]
Diarrhea or colitis, Grade 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. c • Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over > 1 month.

IV = intravenous

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

acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over > 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.
[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged 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 7.
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 T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g. TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 7 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-related hyperthyroidism. [c]
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 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.

Event	Management
	• 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. • Initiate treatment with insulin if needed. • 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.
Hypophysitis pan-hypopituitarism), Grade 2-3	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. [a] • Initiate hormone replacement therapy 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 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. [a] • Initiate hormone replacement therapy if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone, IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 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.

If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.

Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 8.

Table 8 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 1-2 mg/kg/day oral prednisone or equivalent. • 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.
[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of Atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g. in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing 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 9.

Table 9 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist • Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. [a] • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Immune-related myocarditis, Grade 3-4	• 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 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. [a, b] • 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; IV = intravenous.
[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.
[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Infusion Related Reactions

No premedication is indicated for the administration of Cycle 1 of Atezolizumab. However, patients who experience an infusion-related reaction with Cycle 1 of
Atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating Atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis.

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Table 10. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 10 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt Atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue Atezolizumab and contact Medical Monitor. [a]

IRR = infusion-related reaction; IV = intravenous.
[a] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of Atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as
serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 11.

Table 11 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue Atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue Atezolizumab and contact Medical Monitor. c
Immune-related pancreatitis, Grade 2 or 3	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume Atezolizumab. • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. c • Refer patient to gastrointestinal specialist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over > 1 month.

IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.
[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Dermatologic Events

Treatment-emergent rash has been associated with Atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. 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 12.

Table 12 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 10 mg/day oral prednisone or equivalent, 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before Atezolizumab can be resumed.
[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent Atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 13.

Table 13 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue Atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold Atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume Atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding Atezolizumab, permanently discontinue Atezolizumab and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue Atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue Atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1-2 mg/kg/day oral or IV prednisone or equivalent.

IV = intravenous

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

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

[c] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of Atezolizumab. Immune-related meningoencephalitis should be suspected in any 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 14.

Table 14 Management Guidelines for Immune-Related Meningoencephalitis

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

IV = intravenous.
[a] Resumption of Atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with Atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune related Nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal 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. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Table 15 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.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0. a) Atezolizumab may be withheld for a

longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor. b) If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of 10 mg/day oral prednisone before atezolizumab can be resumed. c) Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune related Myositis

Cases of immune related myositis, including biopsy-confirmed cases, were identified in patients that received Atezolizumab. The incidence of myositis observed across the Atezolizumab monotherapy clinical program was <0.1%. There were 4 cases of myositis with a fatal outcome with some cases suggestive of cardiac involvement (myocarditis or AV block). Immune related myositis is considered an important identified risk for Atezolizumab.