EA9161 Frequently Asked Questions
Key Topics for Site Investigators and Staff

This document answers frequently asked questions about EA9161; it is not meant to substitute for the protocol. It is divided into six sections: Eligibility, Required Tests, Treatment, Specimen Submissions, Dose Modifications/Management of Toxicity, and Adverse Event FAQs.

Eligibility

Q1: A diagnosis of Small Lymphocytic Lymphoma (SLL) or Chronic Lymphocytic Leukemia (CLL) is required. How are these terms defined?

For this protocol, SLL and CLL are defined according to the NCI/IWCLL criteria or the WHO criteria. This includes previous documentation of biopsy-proven SLL; or a diagnosis of CLL according to all of the NCI/IWCLL criteria, as follows:

- Peripheral blood lymphocyte count of greater than 5 x10^9/L
- Immunophenotype consistent with CLL defined as:
  - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2)
  - Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)
  - Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) or negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy)

Q2: Is the patient able to receive any prior treatment for CLL or SLL?

Patients cannot have received any prior chemotherapy, BTK inhibitor therapy, venetoclax, small molecule BCR or tyrosine kinase signaling inhibitor, or monoclonal antibody therapy for treatment of CLL or SLL.

Q3: There are several indications for treatment listed in the protocol. How many must the patient meet?

The patient must meet AT LEAST ONE of the following indications for treatment (IWCLL 2018 criteria):

- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10^9/L)
- Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly
- One or more of the following disease-related symptoms:
  - Weight loss ≥ 10% within the previous 6 months
  - Grade 2 or 3 fatigue attributed to CLL
  - Fevers >100.5°F for 2 weeks without evidence of infection
Clinically significant night sweats without evidence of infection
• Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months

Q4: How much time must have passed between prior treatment for other conditions and enrollment?
• No radiation therapy ≤ 4 weeks prior to registration
• No major surgery within 28 days of first dose of study drug; no minor surgery within 3 days of first dose of study drug
• No steroid therapy for anti-neoplastic intent, strong and moderate CYP3A inhibitors/inducers within 7 days prior to first dose of study drug
• No warfarin/another vitamin K antagonist within 30 days of registration
• No other systemic immunosuppressant therapy (other than corticosteroids) within 28 days of the first dose of study drug
• No live, attenuated vaccines within 4 weeks of first dose of study drug (note: this does not include the flu shot, which is permitted at any time)
• Note: Patients with a history of prior malignancy are permitted to enroll, as long as they are not currently receiving treatment for that malignancy (e.g., the malignancy is considered cured)

Q5: Are patients with a Hepatitis B eligible for EA9161?
Per protocol section 3.1.17, positive serology for Hepatitis B is defined as a positive test for HBsAg. If the patient is HBsAg positive, they are ineligible for EA9161. In addition, if negative for HBsAg, but HBeAb positive (regardless of HBsAb status), a Hepatitis B DNA test will be performed and, if positive the subject will be ineligible. If the Hepatitis B DNA test is negative (e.g., viral load undetectable) then the individual is eligible. NOTE: If a patient who is HBsAg negative, HBeAb positive, and Hepatitis B DNA negative is enrolled, they should be considered for either prophylactic anti-viral therapy or careful monitoring for Hepatitis B reactivation.

Q6: Are patients with a positive Coombs test eligible for EA9161?
Patients who have a positive Coombs (direct anti-globulin) test, but no evidence of hemolysis are eligible to participate.

Q7: Are patients with deletion of 17p eligible for EA9161?
Patients cannot have deletion of 17p13 on cytogenetic analysis by FISH. (Note: patients with del17p are ineligible for EA9161, because the ECOG-ACRIN Leukemia Committee and NCI felt that it was unethical to randomize patients with del17p13 to discontinue treatment at 18 months independent of MRD status).

Required Tests

Q8: What is the schedule for pre-study imaging and other required tests and procedures?
Pre-study scans or x-rays used to document measurable or evaluable disease must be done within 2 weeks of registration. Pre-study CBC with differential, LFTs must be done ≤ 2 weeks before registration. All required pre-study chemistries must be done ≤ 2 weeks before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration.

**Q9: What laboratory values are required for registration?**

Specific laboratory values per protocol (GFR, total bilirubin, AST/ALT, and PT/INR) must be obtained within 14 days prior to registration.

**Q10: Does the patient need to be examined at Cycle 3, or will the weekly labs suffice?**

- **Arm A:**
  - Patients must have a physical exam on Day 1 of cycle 3. Physical exams are not required on Cycle 3, day 8, 15, and 22.
  - NOTE: Patients on Arm A must receive a CT scan and CrCl tests at the start of cycle 3, prior to starting venetoclax. A CT scan is only required among Arm A patients who had lymph node ≥ 5 cm in maximal dimension on the baseline CT scan. Tumor lysis risk must also be assessed for Arm A patients at this time.

- **Arm B:**
  - Patients will be seen every 28 days (+/- 4 days) cycles 2-6.

**Q11: Is a CT/PET acceptable in lieu of a CT?**

Yes, CT images from a CT/PET are an acceptable alternative to CT only images.

**Treatment**

**Q12: When should treatment begin after registration?**

Treatment should start within 7 working days after registration.

**Q13: How can study drugs be administered?**

- IV medications in both study arms may be administered via the following methods: peripheral IV, Port-a-cath, central line, PICC, or Hickman.
- Oral medications may be taken before or after obinutuzumab on days where patients are scheduled to receive obinutuzumab infusions. Oral medications should be taken at the same time each day.
- Obinutuzumab is administered at a final concentration of 0.4 mg/mL to 4 mg/ML. Do not use other diluents such as dextrose (5%). Mix diluted solution by gentle inversion.
- Ibrutinib should be taken with 8 ounces of water, swallowed whole. Patients should avoid consuming food and beverages containing grapefruit juice/Seville oranges (this inhibits intestinal cytochrome P450 (CYP) isozyme 3A4 and can increase the concentration of Ibrutinib/venetoclax).
Q14: Does treatment have to be given on the exact scheduled day, or is there some flexibility?

Please refer to protocol Section 5 for details:

- Ibrutinib, scheduled to be given daily for 28 days, can be given +/- 4 days.
- Patients are also scheduled to be seen every 28 days (cycles 1 and 2 for Arm A; Cycles 1-7 for Arm B), but this can be +/- 4 days as well.
- Venetoclax, given for 28 days, cycles 7 and beyond for patients on Arm A, can be given +/-4 days.
- During cycles 8-19, when patients are scheduled to be seen every 90 days, they can be seen +/-7 days.

Q15: Does obinutuzumab require pre-medication?

Unless otherwise indicated, premedication prior to all doses of obinutuzumab (Cycles 1-6) will include the following:

- Methylprednisolone 80 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of obinutuzumab during Cycle 1 days 1 and 2 of therapy. Methylprednisolone should be completed at least 1 hour prior to start of obinutuzumab infusion. Thereafter, it should only be administered to patients with absolute lymphocyte count >25 x 10^9/L, those who had grade 3 or higher infusion reaction(s) with the most recent infusions, or at the treating physician’s discretion.
- Diphenhydramine 50 mg IV or PO (or alternative anti-histamine) and acetaminophen 650 mg PO should be administered 30 minutes prior to obinutuzumab (unless contraindicated) to reduce infusion reactions. Patients with allergic reactions to diphenhydramine and other anti-histamines may have anti-histamines held at the discretion of the treating physician.

Q16: Are growth factors permitted?

Neutrophil growth factors are permitted per ASCO guidelines. Use of colony stimulating factors (e.g., filgrastim, sargramostim, PEG-filgrastim) is permitted during therapy as required for the treatment of febrile neutropenia. Colony stimulating factors may not be used to avoid dose reductions (e.g., to boost counts immediately before starting a treatment cycle).

Q17: Is it common for CLL patients treated with ibrutinib to experience an increase in lymphocytosis?

It is common for CLL patients treated with ibrutinib to experience a transient increased lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis, which may be quite dramatic, is NOT a marker of disease progression or Richter’s transformation and typically resolves over several months. For this reason, no patient on Ibrutinib will be considered to have disease progression based on an increased absolute lymphocyte count that occurs during the first several months of ibrutinib based treatment, unless accompanied by other signs of progression (e.g. enlarging lymph nodes).
Specimen Submissions

Q18: What are the requirements for specimen submissions?
Bone marrow biopsy sections/slides and smears must be submitted at baseline for central histological review. (NOTE: bone marrow biopsy sections/slides must be submitted again at the time of the response evaluation [end of cycle 19]).

- Bone marrow biopsy sections/slides can be from the clinical biopsy performed within three months prior to randomization if the on-study baseline bone marrow biopsy was not performed.
- If a bone marrow aspirate and biopsy are attempted and the aspirate is unsuccessful, the bone marrow biopsy alone is adequate.

Bone marrow aspirate, peripheral blood, and buccal cells are to be submitted (per patient consent) at pre-registration and at designated intervals thereafter according to the protocol’s Sample Submission Schedule.

- All specimens submitted on this trial should be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS).
- Kits are available to order, and will include materials necessary for the preparation and shipment of the specimens (refer to protocol section 10.2 for details).

Q19: When are the Generic Specimen Submission Forms used and where do I find them?
This form is to be completed and submitted with all specimens only if the STS is not available. The form and instructions for its use is located in the protocol, Appendix XV (Pathology Submission Guidelines). Sites should contact the receiving lab to inform them of shipments using this form and need to retroactively log all specimens into STS once the system is available.

Dose Modifications and Management of Toxicity

Q20: What guidance is provided for delay of treatment due to toxicities?

- Patients who experience grade 3 or 4 toxicities on both arms may have their treatment delayed for monitoring of resolution or improvement of toxicity. A dose delay up to 6 weeks (42 days) is permitted to allow recovery of toxicities to grade ≤ 1 or baseline level. If treatment is delayed for more than 6 weeks (42 days), the patients will be withdrawn from study treatment.
- With the exception of hematologic toxicities as described in the protocol (Appendix VIII), all other toxicity grades for dose modification are based on CTCAE v.5.0. In cases where grade 3 or 4 toxicity cannot be attributed to a specific study drug or the attribution is unclear, all suspected study drugs should be stopped regardless of attribution of toxicity until the toxicity is resolved.
- Note: patients discontinuing study treatment for a reason other than disease progression, should remain in the study and continue to have disease assessments per protocol (section 7). If study therapy is interrupted for a reason other than toxicity (e.g., unrelated illness), it must be restarted within 42 days. If interrupted for more than 42 days, study medication should be discontinued permanently.
Q21: Where do I find instructions for modifying the dose of a study drug?

The protocol (section 5.4) details corresponding dose levels for each study drug and guidance when dose modifications are warranted for the following adverse events: neutropenia (including when fever or infection are present); thrombocytopenia; atrial fibrillation; autoimmune hemolytic anemia or thrombocytopenic purpura; tumor lysis syndrome; hepatic impairment, and certain non-hematologic toxicities. Please note that dose adjustments for hematologic toxicity are based on Appendix VIII.

Q22: What are the obinutuzumab infusion reactions, and how are they handled?

• The following side effects may occur during or within 24 hours of any obinutuzumab infusions: shortness of breath, rigors, and other infusion-related toxicities. These have also been noted more frequently in patients with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and emergency response if needed.

• If infusion reactions occur, obinutuzumab infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate.

• If transient bronchospasm occurs, obinutuzumab administration should be interrupted. If these symptoms persist, albuterol (or other B2 agonist) by inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.

• In patients with high total leukocyte counts, close observation for potential toxicities (including tumor lysis syndrome) should occur. In addition, if a marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.

Q23: How should the ibrutinib dose be modified for CYP3A4 inhibitors?

Please refer to the protocol section 8.1.10 for potential CYP3A4/5 interactions, and Appendix X for a list of CYP3A inhibitors and inducers. (Note that a complete list can be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

• Strong and moderate inhibitors of CYP3A4/5 should be avoided while taking ibrutinib/venetoclax (refer to Q24 below).

• If a strong CYP3A4/5 inhibitor must be used, the Medical Monitor should be consulted before the use, and a dose reduction of ibrutinib to 140 mg daily or temporary hold of ibrutinib should be considered. Subjects should be closely monitored for potential treatment-related toxicities when ibrutinib is administered with a strong CYP3A4/5 inhibitor. If Ibrutinib is temporary held or the dose reduced due to administration of strong CYP3A4/5 inhibitors, patients may return to the previous dose of Ibrutinib once they are no longer taking strong CYP3A4/5 inhibitors.

• Moderate CYP3A4/5 inhibitors should be used with caution. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, reduce ibrutinib to 140 mg for
Q24: Can strong or moderate CYP3A or P-gp inhibitors be used if the patient is taking venetoclax?

Avoid concomitant use of strong or moderate CYP3A inhibitors or P-gp inhibitors.
- If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.
- If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

Q25: If the obinutuzumab infusion rate is slowed, and I am unable to complete the day’s scheduled dose, how should the remaining dose be handled?

If < 75% of the dose was given, make the missed part of the dose up the next day. If > 75% of the dose was given, it will be at the physician’s discretion whether to make up the missed part of the dose or omit it.

Adverse Events

Q26: How are expedited adverse events reported?

For EA9161, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. The CTEP-AERS report should NOT be initiated via the CTEP-AERS website.

Q27: Are there any EA9161 specific expedited reporting requirements?

Pregnancies, tumor lysis syndrome, and fungal infections should be reported per protocol.

Q28: When is expedited 24-hour notification required?

For a Serious Adverse Event (SAE) outlined by the six criteria in the protocol AND has an attribution of possible, probable, or definite, the following reporting should be followed:
- All Grade 4 and 5 AEs: 24-hour notification followed by a complete report within 5 calendar days
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization: expedited 10 calendar day report
- Grade 3 AEs