Update #12

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO A041702

A RANDOMIZED PHASE III STUDY OF IBRUTINIB PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX AND OBINUTUZUMAB IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

[X]	**Update:**	[ ]	**Status Change:**
[X]	Editorial/Administrative changes	[ ]	Activation
[ ]	Eligibility changes	[ ]	Closure
[ ]	Therapy/Dose Modifications/Study Calendar changes	[ ]	Suspension
[ ]	Scientific/Statistical Considerations changes	[ ]	Reactivation
[ ]	Correlative Science/BioMS changes		
[X]	Informed Consent changes		
[X]	Other: Updated CAEPR for Venetoclax		

The changes included in this update to A041702 have been made in response to the NCI Action Letter from Dr. Steven Gore (steven.gore@nih.gov). This Action Letter is posted on the A041702 study page on the CTSU website. A revised CAEPR for Venetoclax drug with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate the new risks, consistent with the NCI Model Consent Template instructions.

No recommended level of IRB review is provided by the Alliance as the CIRB is the IRB of record for this trial. This amendment must be implemented within 30 days after posting.

A consent form addendum will need to be signed by all patients currently receiving treatment or having treatment held with Venetoclax. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Title Page

- The Protocol Coordinator contact has been updated.
- The Data Manager contact has been updated.

Section 9.4.3 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for Venetoclax (ABT-199, NSC 766270))

This section has been revised to include the updated venetoclax CAEPR (Version 2.2, July 22, 2025) provided by CTEP. Changes from Version 2.1 to Version 2.2 include the following:

- The SPEER grades have been updated.

- Added New Risk:
  - Rare but Serious: Hepatobiliary disorders - Other (drug-induced liver injury)
  - Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution: Alanine aminotransferase increased; Cataract; Colitis; Creatinine increased; Delirium; Esophageal pain; Esophageal ulcer; Fall; Generalized muscle weakness; Leukemia secondary to oncology chemotherapy; Metabolism and nutrition disorders - Other (hypervolemia); Mucositis oral; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Richter's syndrome); Pain in extremity; Pneumonitis

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution: Back pain; Hyperphosphatemia

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Anemia; Fatigue
  - Changed to Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution from Less Likely: Hypertension; Hypophosphatemia

---

UPDATES TO THE MODEL CONSENT:

What risks can I expect from taking part in this study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for venetoclax:

- Added New Risk:
  - Rare: Damage to the liver which may cause yellowing of eyes and skin, swelling

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Anemia which may require blood transfusion; Tiredness

- Changed to Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): High blood pressure which may cause headaches, dizziness, blurred vision

- Provided Further Clarification:
  - Pain in joints (under Occasional) is now reported as Pain (under Occasional)

INFORMED CONSENT ADDENDUM:

A new informed consent addendum has been added to reflect the new or additional information for Venetoclax with this update. This addendum is intended to be signed by all patients currently receiving treatment or having treatment held with Venetoclax.

A replacement protocol document, model consent, and informed consent addendum have been issued.

This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A041702

A RANDOMIZED PHASE III STUDY OF IBRUTINIB PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX AND OBINUTUZUMAB IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

NCI-supplied agents: Ibrutinib (NSC #748645)
Venetoclax (NSC #766270)
Obinutuzumab (NSC #793436)
IND #: [redacted]
IND Holder: DCTD

ClinicalTrials.gov Identifier: NCT03737981

Study Chair
Jennifer Woyach, MD
The Ohio State University
Tel: 614-685-5667 Fax: 614-293-4812
jennifer.woyach@osumc.edu

Community Oncology Co-chair
Elie Dib, MD
St. Joseph Mercy Hospital
Tel: 734-712-3456
Elie_dib@ihacares.com

Leukemia Correlative Study Co-Chair & Leukemia Correlative Science Committee Chair
John C. Byrd, MD
University of Cincinnati
Tel: 513-558-0858
Byrd2jc@ucmail.uc.edu

Leukemia Committee Co-Chair
Geoffrey L. Uy, MD
Washington University School of Medicine
Tel: 800-600-3606
guy@wustl.edu

Leukemia Committee Co-Chair
Wendy Stock, MD
University of Chicago
Tel: 773-834-8982
wstock@medicine.bsd.uchicago.edu

Cancer in the Older Adults Co-Chair
Aminah Jatoi, MD
Mayo Clinic
Tel: 507-284-4918
Jatoi.aminah@mayo.edu

Pathology Co-Chair
Cecelia Miller, PhD
The Ohio State University
Tel: 614-366-3908
cecelia.miller@osumc.edu

SWOG Study Champion
Brian T. Hill, PhD
Cleveland Clinic
Tel: 216-445-9451
Hillb2@ccf.org

ECOG-ACRIN Study Champion
Wei Ding, MD, PhD
Mayo Clinic
Tel: 507-266-0792
Ding.wei@mayo.edu

Primary Statistician
Jun (Vivien) Yin, PhD
Tel: 507-538-6252
yin.jun@mayo.edu

Cancer in the Older Adults Statistician
Jennifer Le-Rademacher, PhD
Tel:507-284-4402
Le-Rademacher.Jennifer@mayo.edu

Secondary Statistician
Gabriela Perez
Tel: 507-293-9454
Perezburbano.gabriela@mayo.edu

Protocol Coordinator
Jayke Giese
leukemiaprotocols@alliancenctn.org

Data Manager
Korrie Powell
Powell.Korrie@mayo.edu

In Memory of Dr. Arti Hurria

Participating NCTN Groups: Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

Study Resources

Expedited Adverse Event Reporting **http://eapps-ctep.nci.nih.gov/ctepaers/**	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts:

A041702 Nursing Contact
Ilene Galinsky, MSN, ANP-C
Dana-Farber Cancer Institute
Tel: 617-632-3902
Email*: igalinsky@partners.org*

Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital
& Research Institute
300 West 10th Avenue, Lobby
Columbus, OH 43210
Tel: 614-688-4754
AllianceLTB@osumc.edu

A041702 Pharmacy Contact
Caroline Harvey, RPh.
Dana-Farber Cancer Institute
Tel: 617-632-3786
caroline_harvey@dfci.harvard.edu

Drug Distribution Contact
NCI Pharmaceutical Management Branch
Tel: 240-276-6575
PMBAfterHours@mail.nih.gov

Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@allianceNCTN.org
Questions regarding specimens/specimen submissions:	Alliance Hematologic Malignancy Biorepository
Questions regarding drug supply	NCI PMB
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

A RANDOMIZED PHASE III STUDY OF IBRUTINIB PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX AND OBINUTUZUMAB IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Pre-registration eligibility criteria (see Section 3.2) (Step 0)
-CLL or SLL diagnosis
-Central blood submission for correlates & FISH (see Section 6.2)

Registration eligibility criteria (see Section 3.3) (Step 1)
-Diagnosis with CLL or SLL in accordance with 2018 IWCLL criteria
-Intermediate or high-risk Rai stage CLL or SLL
-Criteria met for treatment as defined by 2018 IWCLL guidelines
-No prior therapy for CLL (except palliative steroids or treatment of autoimmune complications per Section 3.3.3)
-Age ≥ 65 years
-ECOG performance status 0-2
-No comorbid conditions or other active diseases per Section 3.3.7
-Not taking concomitant medications as outlined in Section 3.3.8
-No known allergy to mannitol
-No prior significant hypersensitivity to rituximab
-No major surgery within 10 days or minor surgery within 7 days

Required Initial Laboratory Values for Registration (Step 1)

Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3 except if due to bone marrow involvement

Platelet Count (untransfused) ≥ 30,000/mm^3 except if due to bone marrow involvement

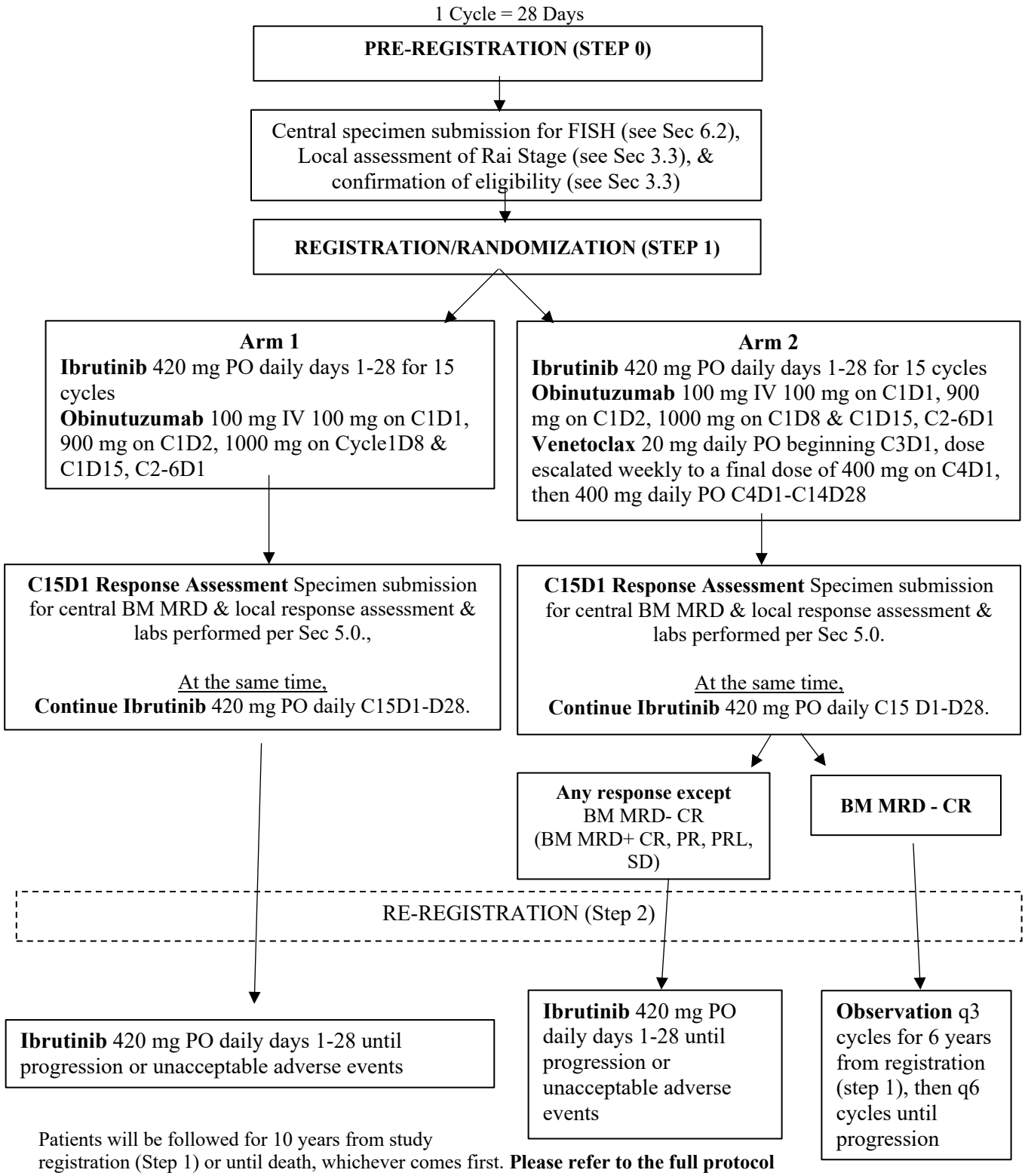
Calc. Creatinine Clearance ≥ 40 mL/min (by Cockcroft-Gault)

Bilirubin ≤ 1.5 x upper limit of normal (ULN) except if due to liver involvement, hemolysis, or Gilbert's disease

AST / ALT ≤ 2.5 x upper limit of normal (ULN) except if due to liver involvement

Re-registration eligibility criteria (See Section 3.4) (Step 2)
- Completion of first 14 cycles of therapy and remain on ibrutinib
- Receipt of central BM MRD results and completion of response evaluation

SCHEMA



Patients will be followed for 10 years from study registration (Step 1) or until death, whichever comes first. **Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan**

Arm 1 Ibrutinib Obinutuzumab

	Cycle 1 D1-28				**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**
	Day 1	**D2**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**									
Ibrutinib	420 mg daily →																	
Obinutuzumab	100 mg	900 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg									

Arm 2 Ibrutinib, Venetoclax, and Obinutuzumab

	Cycle 1 D1-28				**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**C14**	**C15**
	Day 1	**D2**	**D8**	**D15**														
Ibrutinib PO	420 mg daily →																	
Obinutuzumab IV	100 mg	900 mg	1000 mg	1000 mg	Day 1 1000 mg	D1 1000 mg	D1 1000 mg	D1 1000 mg	D1 1000 mg									
Venetoclax PO						20 mg daily, dose escalated weekly*	400 mg daily →											

* Arm 2 Venetoclax Dose Escalation

Cycle 3				**Cycle 4**
Day 1 – 7	D8 - 14	D15-21	D22 - 28	D1 - 7
20 mg	50 mg	100 mg	200 mg	400 mg

Table of Contents

1.0 BACKGROUND

1.1 Initial therapy for CLL in older patients

The optimal initial therapy for older adults with CLL is not established. Ibrutinib is FDA approved in the up-front setting based on data showing excellent activity and durable remissions with this agent [1] as well as the RESONATE-2 study [2], which showed both a PFS and OS advantage for ibrutinib over chlorambucil (median PFS for chlorambucil 18.9 months vs not reached for ibrutinib; 24 month OS 85% for chlorambucil vs 98% for ibrutinib). Response rates were high in this study, with an overall response rate (ORR) of 86% and complete response (CR) rate of 4%. A041202, a randomized phase III trial comparing ibrutinib to standard chemoimmunotherapy (bendamustine plus rituximab) has been completed but results not yet reported, yet the hematology community has adopted ibrutinib as a standard of care for this patient population. This trial and others are also investigating ibrutinib in combination with CD20 antibody compared with ibrutinib as a single agent. While no mature data from randomized studies are available, it is clear that ibrutinib given with CD20 antibody is safe, and is certain to be at least as effective as ibrutinib given as a single agent. Therefore, either ibrutinib alone or in combination with CD20 antibody can be considered a standard of care for the frontline treatment of CLL. Of the clinically available CD20 antibodies, obinutuzumab is the most effective, and can produce complete responses alone and in combination with other agents. To ensure that our standard of care arm is the most effective comparator, we have chosen the combination of ibrutinib and obinutuzumab for this study.

While ibrutinib is highly effective in previously untreated CLL patients, there do remain disadvantage to this therapy. Specifically, the low rate of complete response (CR) and need for continuous administration. While data does not exist to prove that a CR with ibrutinib is superior to a PR, the fact that mutations in B cell specific genes (BTK and PLCG2) are acquired during therapy and drive resistance to this agent [3] suggests that elimination of all CLL cells would decrease the likelihood of mutation acquisition and therefore clinical progression. As well, no data exist relative to discontinuation, even in patients with deep remission. While ibrutinib is generally well tolerated, some toxicities such as hypertension are more common over time, and continuous administration has other obvious disadvantages including cost.

Currently, a number of studies have been designed with the goal of discontinuation of ibrutinib therapy by administration of combinations with either chemotherapy or additional targeted therapies. However, no studies have been undertaken to this point to randomize patients to continue versus discontinue ibrutinib.

1.2 Ibrutinib as Initial Therapy for CLL

1.2.1 Efficacy

Ibrutinib (PCI-32765, Imbruvica™) is a first-in-class, orally-administered, covalently-binding small molecule inhibitor of BTK currently under development for the treatment of B-cell malignancies. Ibrutinib is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL/SLL and Waldenstrom's Macroglobulinemia and for mantle cell lymphoma (MCL) patients who have received at least one prior therapy.

Ibrutinib has been highly effective as initial therapy for CLL. The first study to test this approach, PCYC 1102, showed a 5 year PFS of 92% [4]. As well, the phase III RESONATE-2 study showed a 24 month PFS with this agent. [5] Combinations with ibrutinib and monoclonal antibodies as well have showed exceptional efficacy. In a phase II study of ibrutinib in combination with rituximab for patients with high risk CLL (either treatment-naïve or relapsed), PFS at 18 months was 78%. Another study of ibrutinib in combination with ofatumumab for patients with relapsed disease showed a 12 month PFS

of 83.1%. [6]Overall, these data show that ibrutinib alone or in combination with CD20 monoclonal antibodies produce durable remissions. However, even in the front-line setting, very few patients achieve a complete response, so indefinite duration of therapy is required.

1.2.2 Safety

Ibrutinib alone and in combination with antibodies has consistently demonstrated acceptable safety parameters. In the RESONATE-2 study, the most common adverse events (>20% of patients) included diarrhea, fatigue, nausea, and cough. High grade (grade ≥3) toxicities included hypertension (14%), atrial fibrillation (6%) and bleeding (4%). Discontinuation due to adverse events was relatively rare over the short follow-up. [2]

Long term follow-up of ibrutinib studies has shown relatively few cumulative toxicities, although rate of hypertension does tend to increase over time on drug. [7] Infectious toxicities tend to decrease over time.

1.3 Venetoclax in CLL

1.3.1 Efficacy

Venetoclax has demonstrated considerable efficacy in CLL, both alone and in combination with ibrutinib or monoclonal antibody therapy. In the phase I study in relapsed or refractory CLL, the response rate was 79%. Remarkably, complete remissions occurred in 20% of patients. Median PFS was 25 months in the dose escalation cohort, and 15 month PFS was 66% in the expansion cohort of patients treated at 400 mg daily. [8] Single agent venetoclax has also shown efficacy in patients with relapsed CLL who possess del(17p13.1), where the response rate was 79.4%, with a CR rate of 8%. 12 month PFS was 72%. [9]

Venetoclax has also been studied in combination with monoclonal antibodies. In a phase 1b study of venetoclax in combination with rituximab, OFF was 86%, with a 51% CR rate. Of 25 patients who attained a CR, 80% were minimal residual disease negative. 2 year PFS was 82%. [10] More recently, the MURANO study compared venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL. PFS was superior for venetoclax + rituximab, with 2 year PFS of 82.8%. [11]

1.3.2 Safety

Venetoclax has been well tolerated across studies. In the phase study, adverse events seen in >20% of patients included diarrhea, upper respiratory tract infection, nausea, neutropenia, fatigue, cough, pyrexia, anemia, headache, constipation, and thrombocytopenia. The most significant toxicity seen with venetoclax is tumor lysis syndrome, which occurred in 18% of patients in the phase I setting. This risk has been reduced by slow ramp-up to the desired dose as well as stratification and supportive care based upon tumor lysis syndrome risk. [8]

1.4 Justification for addition of venetoclax

Venetoclax is a rational drug to combine with ibrutinib given preclinical data suggesting synergy [12] [13] as well as extraordinary clinical results as a single agent including impressive CR rates even in the relapsed population. [8] [9] The combination of ibrutinib with venetoclax and obinutuzumab is currently under investigation in the phase I/II setting in both treatment-naïve and relapsed/refractory CLL. 12 patients were initially treated in the Phase Ib portion of the study, where the recommended Phase II dose was determined to be the FDA labeled doses for each drug. [14] There were no dose limiting toxicities, and no patient discontinued therapy.

Toxicities generally were as expected for each drug given individually. The Phase II portion included an additional 50 patients (25 treatment-naïve, 25 relapsed/refractory). Median age was 59, but patients on the study were up to age 77. All toxicities are presented in Table 1 below. Hematologic toxicity was most frequent with the majority of patients experiencing thrombocytopenia (80%) and/or neutropenia (76%). The most frequent non-hematologic toxicities were hypertension (70%), infusion related reactions (66%), bruising (52%), myalgia (50%), and nausea (50%). Grade 3-4 toxicities were largely hematologic with 56% experiencing grade 3-4 neutropenia and 34% grade 3-4 thrombocytopenia. The only frequently occurring non-hematologic grade 3-4 toxicity was hypertension (32%).

The median follow-up for the study was 18.0 months (range 0-24.8) for the RR cohort and 20.6 months (range 7.4-23.9) for the TN cohort. At mid-therapy assessment 23/25 of the RR patients remained on study and all had achieved a response. Three patients achieved CR, 3 a CR with incomplete marrow recovery, and 17 a partial remission. The ORR in RR patients at mid-therapy was 92% (95% CI: 74-99%). Twenty-three (92%) RR patients tested for mid-therapy MRD, with 16 (70%) MRD negative in both the blood and marrow. Two patients had MRD in the blood only, 2 in the marrow only, and 3 in both the blood and the marrow. Mid-therapy responses for the TN cohort have previously been reported (Rogers ASH 2017). To date in 21 (84%) TN patients completed treatment through C14 and 23 (92%) RR remain on study with 21 completing treatment. No patients in either cohort had progressive disease. There was one death from neutropenia and colitis in a TN patient.

Table 1: Treatment related adverse event [1]

ADVERSE EVENT	TN (n=25)			RR (n=25)			ALL (n=50)		
Grade	*1-2*	*3-4*	*Any*	*1-2*	*3-4*	*Any*	*1-2*	*3-4*	*Any*
Platelet count decreased	12 (48)	9 (36)	21 (84)	11 (44)	8 (32)	19 (76)	23 (46)	17 (34)	40 (80)
Neutrophil count decreased	7 (28)	12 (48)	19 (76)	3 (12)	16 (64)	19 (76)	10 (20)	28 (56)	38 (76)
Anemia	4 (16)	-	4 (16)	7 (28)	-	7 (28)	11 (22)	-	11 (22)
Hypertension	10 (40)	10 (40)	20 (80)	9 (36)	6 (24)	15 (60)	19 (38)	16 (32)	35 (70)
Infusion related reaction	19 (76)	-	19 (76)	14 (56)	-	14 (56)	33 (66)	-	33 (66)
Bruising	14 (56)	-	14 (56)	12 (48)	-	12 (48)	26 (52)	-	26 (52)
Myalgia	11 (44)	-	11 (44)	14 (56)	-	14 (56)	25 (50)	-	25 (50)
Nausea	15 (60)	-	15 (60)	10 (40)	-	10 (40)	25 (50)	-	25 (50)
Diarrhea	10 (40)	1 (4)	11 (44)	11 (44)	1 (4)	12 (48)	21 (42)	2 (4)	23 (46)
Dyspepsia	13 (52)	-	13 (52)	9 (36)	-	9 (36)	22 (44)	-	22 (44)
Mucositis oral	13 (52)	-	13 (52)	9 (36)	-	9 (36)	22 (44)	-	22 (44)
Fatigue	10 (40)	-	10 (40)	8 (32)	1 (4)	9 (36)	18 (36)	1 (2)	19 (38)
Arthralgia	8 (32)	1 (4)	9 (36)	9 (36)	-	9 (36)	17 (34)	1 (2)	18 (36)
AST increased	6 (24)	1 (4)	7 (28)	11 (44)	-	11 (44)	17 (34)	1 (2)	18 (36)
Hyperuricemia	8 (32)	1 (4)	9 (36)	9 (36)	-	9 (36)	17 (34)	1 (2)	18 (36)
Rash maculo-papular	11 (44)	-	11 (44)	5 (20)	-	5 (20)	16 (32)	-	16 (32)
Weight gain	9 (36)	-	9 (36)	4 (16)	-	4 (16)	13 (26)	-	13 (26)
ALT increased	2 (8)	1 (4)	3 (12)	9 (36)	-	9 (36)	11 (22)	1 (2)	12 (24)
Blood bilirubin increased	7 (28)	-	7 (28)	4 (16)	-	4 (16)	11 (22)	-	11 (22)
Hypocalcemia	7 (28)	-	7 (28)	4 (16)	-	4 (16)	11 (22)	-	11 (22)
Chills	7 (28)	-	7 (28)	2 (8)	-	2 (8)	9 (18)	-	9 (18)

*Treatment-related adverse events occurring in ≥25% of patients in either cohort. AST = Aspartate aminotransferase. ALT = Alanine aminotransferase.

Based on previous trials showing a survival advantage for initial therapy even in the setting of active agents for second line therapy, [2] [15] we believe that investigation of a combination of our most active agents in the up-front setting is justified. As a secondary endpoint this trial will collect OS data.

1.5 Justification for Correlative Studies

Limited data exist in the treatment-naïve setting to inform how traditional (cytogenetics, IGHV mutational status) or novel (DNA mutations) prognostic studies impact response to ibrutinib/obinutuzumab or ibrutinib/obinutuzumab/venetoclax in the front-line setting. With the high response rates and durable remissions seen with these combinations, it will require a large trial with extended follow up to gather meaningful data. Therefore, this study has the unique opportunity to collect biomarkers that will impact our understanding of prognostic studies associated with these drugs. As well, there are no data to determine mechanisms of resistance associated with ibrutinib/obinutuzumab/venetoclax, and again the efficacy of this agent makes a large study required to begin to understand these mechanisms. Because the importance of the data to be obtained is so high, and risk to the patients is minimal, correlative laboratory studies will be required for all patients.

1.6 Impact of the trial

The proposed trial will establish the standard of care for initial therapy of older adults with CLL. It also has the potential to diminish drug costs significantly for patients who attain BM MRD- status and can go off therapy. As well, data regarding discontinuation of ibrutinib is applicable to the relapsed setting as well as other diseases where ibrutinib is used.

2.0 OBJECTIVES

2.1 Primary objective

To compare the progression-free survival (PFS) between control treatment and experimental treatment strategies: ibrutinib/obinutuzumab (IO) with ibrutinib maintenance (IM) versus ibrutinib/venetoclax/obinutuzumab (IVO) regardless of IM or observation.

2.2 Secondary objectives

2.2.1 To compare BM MRD- CR rates, MRD- rates, and depth of response, and depth of response at Cycle 15 Day 1 between patients treated with IO versus IVO.

2.2.2 To compare overall survival (OS) between the control and experimental treatment strategies: IO with IM versus IVO regardless of IM or observation.

2.2.3 To compare the 5-year PFS and OS for the control and experimental treatment strategies: IO with IM versus IVO regardless of IM or observation.

2.2.4 To describe the toxicity profile for each of the treatment strategies and by each treatment course.

2.3 Correlative science objectives

2.3.1 To compare MRD status between blood and bone marrow at the end of induction treatment/Cycle 15 Day 1 to determine whether blood MRD can be used as a surrogate to bone marrow MRD with these treatment regimens.

2.3.2 To compare peripheral blood MRD status by standard central flow cytometry to next generation sequencing (NGS) using ClonoSeq technique to determine the agreement in MRD negativity of the two techniques.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-study guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients may not have an active intercurrent disease or concurrent malignancy that is expected to limit survival to <5 years.
- Patients who cannot swallow oral formulations of the agents.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for women 18 months after obinutuzumab treatment and for men 180 days after obinutuzumab treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-registration eligibility criteria (Step 0)

___ 3.2.1 CLL or SLL diagnosis

Patients must have been diagnosed with CLL (> 5000 B-cells per uL of peripheral blood at any point during the course of their disease) or Small lymphocytic lymphoma (SLL) with <5000 B-cells per μL of blood but with disease-associated lymphadenopathy.

___ 3.2.2 Central FISH blood submission

This blood submission is mandatory prior to registration/randomization to perform FISH centrally that will be used for stratification. It should be obtained as soon after pre-registration as possible. See Sections 4.4 and 6.2 for more information.

3.3 Registration eligibility criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ 3.3.1 Documentation of disease

Patients must be diagnosed with CLL or SLL in accordance with 2018 IWCLL criteria [28] that includes all of the following:

- $\geq 5x10^9$ B lymphocytes (5000/μL) in the peripheral blood measured by flow cytometry at any point in the course of the disease or less peripheral blood involvement but disease-associated lymphadenopathy.
- On local morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes.
- Neoplastic cells on immunophenotype (performed locally) must reveal a clonal B-cell population, which express the B cell surface markers of CD19 and CD20, as well as the T-cell antigen CD5. Patients with bright surface immunoglobulin expression or lack of CD23 expression in >10% of cells must lack t(11;14) translocation by interphase cytogenetics.

___ **3.3.2 Staging and indication for therapy**

- Patients must be intermediate or high-risk Rai stage CLL or SLL

Intermediate Risk (Formerly Stage I/II)	Lymphadenopathy and/or hepatomegaly or splenomegaly without anemia or thrombocytopenia
High Risk (Formerly Stage III/IV)	Splenomegaly and/or Anemia (hemoglobin <11g/dL) not attributable to autoimmune hemolytic anemia and/or Thrombocytopenia (plt <100 x109/L) not attributable to autoimmune thrombocytopenia

- Patients must meet criteria for treatment as defined by 2018 IWCLL guidelines[16] which includes at least one of the following criteria:
  - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
  - Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
  - Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
  - Progressive lymphocytosis with a lymphocyte doubling time < 6 months or an increase of ≥ 50% over a 2 month period
  - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
  - Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, spine)
  - Constitutional symptoms, which include any of the following:
    - Unintentional weight loss of 10% or more within 6 months
    - Significant fatigue

- Fevers >100.5 degrees F for 2 weeks or more without evidence of infection
- Night sweats ≥1 month without evidence of infection

___ **3.3.3 Prior treatment**

- Patients must not have had prior therapy for CLL/SLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids).
- Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL/SLL must be complete at least 4 weeks prior to enrollment. Palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration.

___ **3.3.4 Age ≥ 65 years**

___ **3.3.5 ECOG performance status 0-2**

___ **3.3.6 Required initial laboratory values**

Absolute Neutrophil Count (ANC)	≥ 1,000/mm3 except if due to bone marrow involvement
Platelet Count (untransfused)	≥ 30,000/mm3 except if due to bone marrow involvement
Calc. Creatinine Clearance	≥ 40 mL/min (by Cockcroft-Gault)
Bilirubin	≤ 1.5 x upper limit of normal (ULN) except if due to liver involvement, hemolysis, or Gilbert's disease
AST / ALT	≤ 2.5 x upper limit of normal (ULN) except if due to liver involvement

___ **3.3.7 Comorbid conditions or other active diseases**

- Patients must not have any history of Richter's transformation or prolymphocytic leukemia (prolymphocytes in blood > 55%).
- If evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy if indicated.
- Please note: IVIG can cause a false positive hepatitis B serology. If patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B DNA) they may still participate in the study, must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.
- If history of hepatitis C virus (HCV) infection, must be treated with undetectable HCV viral load
- Patients with Class III or Class IV heart failure by New York Heart Association, those with unstable angina, and those with uncontrolled arrhythmia are not eligible.
- Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months are not eligible.

- Human immunodeficiency virus (HIV)-infected patients on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial

___ **3.3.8 Concomitant medications**

- Patients must not be receiving active systemic anticoagulation with heparin or warfarin. Patients on warfarin must discontinue the drug for at least 10 days prior to registration on the study.
- Chronic concomitant treatment with strong inhibitors of CYP3A4/5 is not allowed on this study. Patients on strong CYP3A inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1.9 for more information.
- Chronic concomitant treatment with strong CYP3A4/5 inducers is not allowed. Patients must discontinue the drug 14 days prior to registration on the study. See Section 8.1.10 for more information.
- Patients must not require more than 20 mg prednisone or equivalent corticosteroid daily.
- Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics.

___ **3.3.9 Central FISH blood results**

Central FISH blood results are mandatory prior to registration/randomization for it will be used for stratification. See Sections 4.4 and 6.2 for more information.

___ **3.3.10 Other**

- Patients must be able to swallow capsules and not have the following conditions: disease significantly affecting gastrointestinal absorption, resection of the stomach or small bowel, partial or complete bowel obstruction.
- Patients must not have a known allergy to mannitol.
- Patients must not have prior significant hypersensitivity to rituximab (not including infusion reactions).
- Patients may not have had major surgery within 10 days prior to registration, or minor surgery within 7 days prior to registration. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration for a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.
- Patients must be able to receive either a xanthine oxidase inhibitor or rasburicase for prophylaxis/treatment of TLS.

3.4 Eligibility criteria for re-registration (Step 2)

___ **3.4.1 Completion of treatment through Cycle 14 Day 28, and remain on ibrutinib therapy.**

___ **3.4.2 Receipt of central BM MRD results.**

___ **3.4.3 Response assessment completed per** Section 5.0**.**

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

IVR—MD, DO, or international equivalent;

NPIVR—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

AP—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges

Associate (A)—other clinical site staff involved in the conduct of NCI-sponsored trials; and

Associate Basic (AB)—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

Addition to a site roster;

Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;

Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;

- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Downloading site registration documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;

- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A041702*.
- Click on *Documents, Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration to* download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting regulatory documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

4.2.4 Checking site registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.3 Patient pre-registration requirements (Step 0)

Informed consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

4.4 Patient registration requirements (Step 1)

Pre-registration (Step 0) completed: All patients are REQUIRED to be pre-registered to A041702 in order to complete patient registration (Step 1) and to submit peripheral blood to the Alliance Hematologic Malignancy Biorepository (HEME) for FISH to be performed at The Ohio State University (see Section 6.2), with FISH results used for stratification. After patient pre-registration with specimen submission, sites will be notified of FISH results via email within 7-10 business days of specimen receipt at the Alliance Biorepository (HEME). Once patient registration eligibility is confirmed (See Section 3.3) the patient may be registered (Step 1) in OPEN. Registration must occur within 36 business days of receipt of FISH results.

FISH for stratification: All patients are REQUIRED to be pre-registered to A041702 in order to submit peripheral blood to the Alliance Hematologic Malignancy Biorepository (HEME) for FISH performed at The Ohio State University (see Section 6.2.2). The FISH results will be used for stratification.

4.5 Patient re-registration requirements (Step 2)

- **Day 1 of Cycle 15 response assessment:** The patient must have successfully completed fourteen cycles of therapy on Arm 1 (Ibrutinib/Obinutuzumab) or Arm 2 (Ibrutinib/Venetoclax/Obinutuzumab) and remain on ibrutinib therapy in order to be re-registered. Response assessment should be performed per Section 5.0 and specimens submitted per Section 6.2. Re-registration should be performed by Cycle 15 Day 21 to allow for agent ordering and provision by CTEP (see Section 10.1).
- All patients are required to submit blood and bone marrow for central MRD. Sites will be notified of bone marrow MRD results via email within 7-10 business days of specimen receipt at Alliance HEME Biorepository. Response assessment (including CT) must be performed per Section 5.0. Follow OPEN enrollment procedures as detailed in Section 4.7 to register the patient to Step 2. Sites will be notified via email of the treatment assignment according to the following:
    - **Patients randomized to Arm 1:** At re-registration, these patients will be automatically assigned to ibrutinib maintenance
    - **Patients randomized to Arm 2 who are determined to have any response except BM MRD- (centrally) CR (locally):** At re-registration, these patients will be automatically assigned to ibrutinib maintenance.
    - **Patients randomized to Arm 2 who are determined to be BM MRD- (centrally) and determined to be CR (locally):** At re-registration, these patients will be automatically assigned to observation.

4.6 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.7 Stratification Factors and Treatment Assignments

Step 1 randomization:

- Rai stage (intermediate vs. high)
- High-risk FISH abnormality del(17p13.1) (present vs. absent).

Step 2 re-registration:

- Initially randomized to Arm 1
- Initially randomized to Arm 2 and any response except BM MRD- CR
- Initially randomized to Arm 2 and a response of BM MRD- CR

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- Peripheral blood flow cytometry to meet pre-registration eligibility criteria (see Section 3.2.1) may be completed at any time prior to pre-registration.
    - IGHV mutational status needs to be performed prior to registration, but results are not required to register the patient. May be completed any time prior to registration
- To be completed ≤ 14 DAYS before registration: All laboratory studies (except those listed below), history and physical.
- To be completed ≤ 60 DAYS before registration: Peripheral blood and bone marrow flow cytometry, bone marrow aspirate and biopsy, CT scan, HBsAg, HBsAb, Hep C, HB core antibody, Serum immunoglobulins, Beta 2 microglobulin. If a bone marrow biopsy was performed as standard of care within this window, a repeat is not necessary and no research aspirate needs to be sent.

	Prior to Pre-Reg	**Prior to Reg**	**C1 D1**	**C2-6 D1**	**C9 D1, C12 D1, C15 D1**	**C16D1, then D1 q 3 cycles for 6 years from registration (Step 1), then q 6 cycles***	**Clinical follow-up ******	**Clinical disease progression *****
Tests & Observations******								
History & progress notes		X		X	X	X	X	X
Physical examination and node measurements		X		X	X	X	X	X
Height		X						
Weight / body surface area		X	X	X	X	X		X
Performance status		X	X	X	X	X		X
Solicited baseline abnormalities/AEs		X	X	X	X	X		X
Laboratory Studies******								
Complete blood count (CBC)		X	X	X	X	X	X	X
Serum creatinine, BUN		X	X	X	X	A		
Serum electrolytes (Na/K)		X	X	X	X			
Uric acid / phosphate / Ca^{++F}		X	X					G
AST, ALT, alk. phos., bilirubin, albumin		X		X	X	A		
LDH		X	X	X	X			X
Beta-2-microglobulin		X						
Direct antiglobulin test (Coomb's test)		X						
HBsAg, HBsAb, Hep C, HB core antibody		X(1)						

Serum immunoglobulins (IgG, IgA, IgM)		X		B	B	C	C	
IGVH mutational status	X							
TLS risk assessment			D					
Venetoclax TLS monitoring labs				E				
Staging**								
Peripheral whole blood for central FISH & cytogenetics		X(2)						
CT scan (chest, neck, abdomen, & pelvis) & bilateral measurements of largest nodes		X		B(3)	B	C	C	X
Peripheral blood flow cytometry	F	F(4)		B(4)	B(4)	X(4)		X(4)
Bone marrow aspirate (including flow cytometry) & biopsy		X(5)		B	B			
Peripheral whole blood and bone marrow aspirate for central BM MRD				B	B			
Correlative studies: (Mandatory for all patients)								
Peripheral whole blood, bone marrow aspirate and buccal samples for correlative studies	*Whole blood required prior to registration, at the end of treatment during Day 1 of Cycle 15,Day 1 of Cycle 22, every Day 1 of 6 cycles beginning C22 until 6 years from registration (Step 1), then every 12 cycles, at discontinuation of treatment, and relapse/progression. Bone marrow aspirate required prior to registration, at the end of initial treatment Day 1 of Cycle 15, and at discontinuation of treatment. If bone marrow was performed as standard of care prior to study pre-registration but within the time window, research aspirate does not need to be sent. Buccal cell sample required prior to treatment. See Section 6.2*							

* Testing schedule is Cycle 16 Day 1, then on Day 1 of every 3 cycles until 6 years after the date of study registration (Step 1), then on Day 1 of every 6 cycles until progression, or 10 years from study registration, whichever occurs first. Following the completion of therapy, each cycle has a window of +/- 14 days.

** Clinical follow-up is defined for patients who discontinue protocol therapy (either prior to re-registration or after re-registration with ibrutinib) in the absence of clinical disease progression to CLL (see Section 12.3.2 for definition and requirements). Clinical follow-up is required every 3 cycles (from date of discontinuation of protocol therapy) until 6 years have elapsed from study registration (Step 1), then every 6 cycles thereafter until progression, or until 10 years from study registration, whichever occurs first. Each of these observations has a +/- 30 day window.

*** After documentation of clinical disease progression to CLL, survival follow-up is required every 6 months until death or 10 years have elapsed from registration (Step 1), whichever occurs first.

**** Tests & observations and laboratory studies can be performed +/- 7 calendar days to Day 1 of the specified cycle. CT scans and bone marrow biopsy may be completed +/- 7 calendar days from the beginning of the specified cycle.

1 All patients should be screened for hepatitis B prior to registration. Patients who test positive for hepatitis B should be screened with hepatitis B DNA testing every 3 cycles and should be considered for prophylactic antiviral therapy.

2 Peripheral whole blood for central FISH testing is required for all patients at the pre-registration assessment. Results must be received in order to register the patient.

3 CT scans for high TLS risk patients should be repeated prior to C3D1 if treating physician thinks patient may no longer fall in the high-risk category; if low/med risk, treatment should be modified accordingly.

4 Peripheral blood flow cytometry must include an assessment of number of CLL cells per uL, absolute B-cell counts (CD19+ & CD5+), and T-cell count.

5 Bone marrow aspirate at baseline should include flow cytometry. Panel should include: assessment of number of CLL cells per uL, absolute B-cell counts (CD19+ & CD5+), and T-cell count. If bone marrow biopsy was completed within the timeframe but prior to study participation and the flow cytometry was not included, the bone marrow does not need to be repeated.

A For patients who continue on ibrutinib therapy only.

B For patients who complete Cycles 1-14, perform only on Cycle 15 Day 1. For patients who discontinue protocol therapy in Cycles 1-14 for reasons other than clinical disease progression to CLL, perform only at the end of treatment during Step 1 (+/- 14 calendar days). Local flow cytometry is only required on baseline bone marrow (not at Cycle 15 Day 1).

C Perform every 12 cycles. For all patients, including those assigned to ibrutinib and those assigned to Observation after re-registration, perform on Day 1 of Cycles 28, 40, etc. For patients in clinical follow-up, perform every 12 cycles beginning with the initial response assessment after therapy discontinuation. Obtain immunoglobulins during follow-up as clinically indicated.

D Venetoclax risk assessment is required C1D1. Requirements are outlined in Section 7.1.2. If the treating physician suspects that risk category has changed prior to day 1 of venetoclax (due to ibrutinib/obinutuzumab), CT scans may be repeated and risk reassessed prior to venetoclax administration.

E Venetoclax TLS monitoring labs include creatinine, potassium, calcium, uric acid, and phosphate. These labs must be performed on Cycle 3 Days 1, 8, 15, 22 and Cycle 4 Day 1. These tests should be performed on the schedule outlined in Section 7.1.2.

F Perform prior to pre-registration rather than prior to registration if diagnosis of CLL has not already been confirmed.

G Obtain serum uric acid, phosphate, and calcium during follow-up as clinically indicated.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.1 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation as outlined below:

- Baseline: Peripheral blood flow and bone marrow report, H&P with lymph node sizes documented on physical exam, and CT report. The Central FISH Review results form is to be added as 'Other' supporting documentation.
- Cycle 15 Day 1: Peripheral blood flow and bone marrow report, H&P with lymph node sizes documented on physical exam, CT report; if protocol therapy is discontinued during Cycles 1-14 for reasons other than clinical disease progression to CLL, submit instead at the end of treatment (+/- 14 calendar days). The Central Bone Marrow and Peripheral Blood MRD results are to be added as 'Other' supporting documentation.
- C16D1 and every third cycle after C15D1 response assessment: Peripheral blood flow reports
- Every 12 cycles after C16D1: CT reports
- Progression (Either before or after C15D1 response assessment): H&P with lymph node sizes documented on physical exam, CT report, and, if performed, bone marrow report.

Supporting documentation is to be submitted via Rave.

6.1.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Specimen collection and submission

The Alliance A041702 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be address to the contacts specified in the manual.

For all patients registered to Alliance A041702: Submission of blood for central FISH testing is required for all patients at the pre-registration assessment and prior to registration. Submission of bone marrow and blood for central BM MRD for Cycle 15 Day 1 assessment is required for all patients; if protocol therapy is discontinued during Cycles 1-14 for reasons other than clinical disease progression to CLL, submit within 14 days of discontinuation of therapy.

	Prior to registration	Day 1 Cycle 15 *	Day 1 q 6 cycles Beginning C22 until 6 years from registration (Step 1), then q 12 cycles**	Discontinuation of Treatment***	Relapse/ Progression ****
Mandatory for <u>all</u> patients registered to A041702:					
Bone marrow aspirate (EDTA/lavender top)	10 mL	10 mL[2]		10 mL	
Peripheral blood (acid citrate dextrose/ ACD-A)	40 mL	40 mL	40 mL	40 mL	40 mL
Peripheral blood (sodium heparin)	5 mL[1]	5 mL	5 mL	5 mL	5 mL
Buccal cell sample (kit provided)	X				

* For patients who have completed 14 cycles of treatment, bone marrow and peripheral blood may be submitted +/- 7 business days from Cycle 15 Day 1.

** Submit +/- 7 business days.

*** For patients who have discontinued treatment during Cycles 1-14 for reasons other than clinical disease progression to CLL,1, blood and bone marrow must be submitted within +/- 14 business days of discontinuation of therapy.

**** The relapse/progression specimen is not required if the discontinuation of therapy specimen submissions were submitted within the previous 2 months.

1 Peripheral whole blood for central FISH testing is required for all patients at the pre-registration assessment and within 36 business days prior to registration.

2 MRD assessment will be performed, and the specimen MUST be submitted no later than 7 business days after Day 1 of Cycle 15 to allow for re-registration by Cycle 15 Day 21 and for agent ordering and provision by CTEP (Section 10.1). See Section 4.6 for more information.

7.0 TREATMENT PLAN/INTERVENTION

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual antibody doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of therapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. New cycles of ibrutinib can be started

up to 7 days before the protocol-defined date for major life events. Documentation to justify this delay should be provided.

7.1 Cycle 1 through Cycle 14 Day 28

Prior to registration, all patients should meet eligibility criteria and undergo centralized FISH testing. Central FISH results as well as Rai stage must be documented on the enrollment form. After registration, the institutional contact will receive a registration confirmation and treatment registration that includes the randomization arm.

Protocol treatment is to begin ≤ 14 days after registration (Step 1).

7.1.1 Arm 1: Ibrutinib/Obinutuzumab

Treatment on Arm 1 consists of ibrutinib 420 mg PO daily on days 1-28 of each of fifteen 28-day cycles. Obinutuzumab is administered IV at 100 mg on cycle 1 day 1, 900 mg on cycle 1 day 2, 1000 mg cycle 1 days 8 and 15, and 1000 mg day 1 of cycles 2-6.

- Recommended/prohibited ancillary therapy is outlined in Section 8.1.
- Premedication: No premedication is required for ibrutinib. Premedication for obinutuzumab per institutional guidelines is permitted, however, recommended premedication is the following:
    - 20 mg dexamethasone IV or 80 mg methylprednisolone IV at least 1 hour prior (first 2 doses, then may be discontinued at treating physician discretion).
    - 650-1000 mg acetaminophen at least 30 minutes prior.
    - Anti-histamine (e.g. 50 mg Benadryl) at least 30 minutes prior (first 2 doses, then may be discontinued at treating physician discretion).
- Tumor Lysis Syndrome (TLS), including fatal cases, has been reported in patients receiving obinutuzumab. Patients with high tumor burden, high circulating lymphocyte count (>25 x 10 9 /L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab.
- During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS per institutional standards. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.
- Drug administration: Full administration guidelines are outlined in Section 10.1. Ibrutinib should be administered at least 30 minutes prior to obinutuzumab on cycle 1 day 1. Thereafter, the order of administration may be altered per institutional guidelines.
- Patients on ibrutinib should keep a daily drug administration record with dates and times taken (see Appendix IV, Patient Medication Diary).
- If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to normal schedule the following day. The patient should not take extra capsules to make up the missed dose, and any remaining study drug must be returned at the next scheduled visit.

- Dose modifications/dose delays after cycle 1 are outlined in Section 8.2.

7.1.2 Arm 2: Ibrutinib/Venetoclax/Obinutuzumab

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each of 15 28-day cycles. Obinutuzumab is administered IV at 100 mg on cycle 1 day 1, 900 mg on cycle 1 day 2, 1000 mg cycle 1 days 8 and 15, and 1000 mg day 1 of cycles 2-6. Venetoclax is taken PO starting at 20 mg daily on cycle 3 day 1, and dose escalated once weekly (50 mg starting C3D8, 100 mg starting C3D15, 200 mg starting C3D22, 400 mg starting C4D1) to a final dose of 400 mg daily beginning on cycle 4 day 1 and continuing to the end of cycle 14. Venetoclax should be taken with a meal (and both venetoclax and ibrutinib should be taken with water).

- Recommended/prohibited ancillary therapy is outlined in Section 8.1.
- Premedication:
  - No premedication is required for ibrutinib.
  - Venetoclax premedication TLS prophylaxis is shown in Table 2 below.
  - Premedication for obinutuzumab per institutional guidelines is permitted, however, recommended premedication is as follows:
    - 20 mg dexamethasone IV or 80 mg methylprednisolone IV at least 1 hour prior (first 2 doses, then may be discontinued at treating physician discretion).
    - 650-1000 mg acetaminophen at least 30 minutes prior.
    - Anti-histamine (e.g. 50 mg Benadryl) at least 30 minutes prior (first 2 doses, then may be discontinued at treating physician discretion).
- Tumor Lysis Syndrome (TLS), including fatal cases, has been reported in patients receiving obinutuzumab. Patients with high tumor burden, high circulating lymphocyte count (>25 x 10 9 /L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab.
- During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS per institutional standards. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.
- Drug administration: Ibrutinib should be administered at least 30 minutes prior to obinutuzumab on cycle 1 day 1. Venetoclax should be given at least 60 minutes prior to obinutuzumab. Thereafter, the order of administration may be altered per institutional guidelines.
- A 2-hour window is allowed for the 24-hour post dose draw required with each venetoclax ramp up in C3/ARM2. For the earlier draws (within 12 hours post dose), a 1-hour window is allowed.

- Venetoclax TLS risk category will be assessed at C1D1 according to the guidelines in Table 2 below. For patients at high risk for TLS or those at medium risk with CrCl <80ml/min, the first dose of 20 mg venetoclax and 50 mg venetoclax should be administered in the hospital setting. If desired by the treating physician, risk category assessment can be repeated prior to C3D1. Patients who are initially at high or medium risk but then decrease risk upon reassessment can be treated as an outpatient. Patients can be discharged after review of 24-hour post dose labs and if no evidence of TLS.
- Patients on ibrutinib and venetoclax should keep a daily drug administration record with dates and times taken (see Appendix IV and Appendix V, Patient Medication Diary).
- If a dose of ibrutinib or venetoclax is missed, it can be taken as soon as possible on the same day (< 8 hours after the missed dose) with a return to normal schedule the following day. Vomited doses should not be made up. Any remaining study drug must be returned at the next scheduled visit. Dose modifications/dose delays after cycle 1 are outlined in Section 8.2.

Adapted from Venetoclax package insert:

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5- week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

Table 2 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumor burden determination from clinical trial data.

Table 2. Recommended TLS Prophylaxis Based on Tumor Burden from Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumor Burden	Prophylaxis	Blood Chemistry Monitoring[c,d]

		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp- up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp- up doses • Consider hospitalization for patients with CrCl <80ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.
[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax. [c]Correct abnormal blood chemistries prior to administering venetoclax
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

7.1.3 Cycle 15 Day 1 through Cycle 15 Day 28

Following the completion of 14 cycles, all patients will receive a 15th cycle of ibrutinib therapy as they undergo restaging and response assessment including central evaluation of BM MRD. See sections 4.5, 5.0 and 6.2 for more information. All patients are required to re-register (Step 2). Patients will be assigned follows to subsequent treatment beginning Day 1 of Cycle 16 as follows:

- All patients initially randomized to Arm 1 Ibrutinib/Obinutuzumab will be assigned to Ibrutinib.
- All patients initially randomized to Arm 2 (Ibrutinib/Venetoclax/Obinutuzumab) and who do not achieve a BM MRD negative CR will be assigned to Ibrutinib.
- Patients who are initially randomized to Arm 2 (Ibrutinib/Venetoclax/Obinutuzumab) and who do achieve a BM MRD negative CR will be assigned to Observation.

7.2 After Cycle 15 Day 28

7.2.1 Ibrutinib

Treatment on this arm will consist of ibrutinib 420 mg daily starting cycle 16 day 1 and continuing until disease progression or until criteria in Section 12.1 are met.

7.2.2 Observation

Treatment on this arm will consist of observation every 3 cycles for 6 years from registration (84 cycles), then every 6 cycles thereafter until disease progression, until criteria in Section 12.1 are met, or 10 years from study registration (whichever comes first)

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other agent which would be considered treatment for CLL or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. All blood products should be irradiated and leukopore filtered to prevent transfusion-associated graft versus host disease. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records. Monoclonal antibodies to treat or prevent COVID-19 are allowed on the study.

8.1.3 No infectious prophylaxis is required for the administration of ibrutinib or venetoclax but may be administered if consistent with institutional guidelines. Premedication for TLS with venetoclax dose escalation is outlined in Table 2 in Section 7.1.2. Institutional guidelines regarding supportive care related to obinutuzumab infusions should be utilized. Patients with absolute lymphocyte count >25,000/µL should receive prophylaxis with allopurinol for at least 7 days prior to the start of therapy. A suggested regimen for premedication for obinutuzumab is provided below:

- 20 mg dexamethasone IV or 80 mg methylprednisolone IV at least 1 hour prior (first 2 doses, then may be discontinued at treating physician discretion).
- 650-1000 mg acetaminophen at least 30 minutes prior.
- Anti-histamine (e.g. 50 mg Benadryl) at least 30 minutes prior (first 2 doses, then may be discontinued at treating physician discretion).

8.1.4 Lymphocytosis

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (>400000/mcL) may confer increased risk. These patients should be closely monitored. Administer supportive care such as hydration

and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of leukostasis symptoms, and then ibrutinib can be restarted.

8.1.5 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.6 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

White Blood Cell Growth Factors (Includes: filgrastim (G-CSF), pegfilgrastim tbo-filgrastim, and sargramostim (GM-CSF)) and other FDA approved white blood cell growth factor biologics) may not be used prophylactically to avoid dose reductions, delays or to allow for dose escalations specified in the protocol, but may be used in cases of prolonged or recurrent neutropenia or in a patient who has had neutropenia with previous cycles. If White blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.1.8 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions as per institutional standards.

8.1.9 CYP3A Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A is not recommended. Strong CYP3A inhibitors are contraindicated with ibrutinib at all times. Ibrutinib should be dose reduced to 140 mg daily when administered with a moderate CYP3A inhibitor. Strong CYP3A inhibitors are also contraindicated during the venetoclax ramp up and must be used with caution during steady state venetoclax dosing. Venetoclax dose should be reduced by 75% if administered with a strong CYP3A inhibitor and by 50% if administered with moderate CYP3A inhibitors or with P-gp inhibitors.

The following drugs are EXAMPLES of strong inhibitors of CYP3A and are not allowed during treatment with ibrutinib.

Boceprevir	Clarithromycin	Cobicistat	Idelalisib
Conivaptan	Danoprevir/Ritonavir	Elvitegravir/Ritonavir	Indinavir

Itraconazole	Ketoconazole	Mibefradil	Lopinavir/Ritonavir
Nefazodone	Nelfinavir	Ritonavir	Paritaprevir/Ritonavir combindations
Posaconazole	Saquinavir	Telaprevir	Telithromycin
Tipranavir/Ritonavir	Voriconazole		

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

Grapefruit and Seville oranges may increase ibrutinib and venetoclax plasma concentrations and should be avoided for the duration of ibrutinib therapy.

8.1.10 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A and are not allowed during treatment with ibrutinib or venetoclax.

- Rifampin
- Carbamazepine
- Avasimibe
- Enzalutamine
- Mitotane
- Phenytoin
- St. John's wort

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.11 Surgery

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis)

ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, or for at least 7 days after the urgent surgical procedure, whichever is longer.

8.1.12 Permitted Concomitant Medications

- Short courses (<4 weeks) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.
- Treatment for autoimmune cytopenias are permitted for <4 weeks at doses that do not exceed 100 mg per day of prednisone or equivalent.
- The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

8.1.13 Other malignancies

Patients diagnosed with other malignancies may remain on therapy in many cases. Therapy may always be continued during workup for another cancer and until the initiation of new therapy. In general, patients may continue therapy if the therapy for another cancer includes surgery, radiation, or hormonal therapy. Please contact the study chair in individual cases to determine whether protocol therapy can continue.

8.1.14 Hepatitis B Reactivation

Hepatitis B reactivation has been reported with obinutuzumab as well as ibrutinib. Patients with chronic hepatitis B are eligible for the protocol as long as viral load is undetectable. These patients should be monitored every 3 cycles for hepatitis B reactivation with hepatitis B DNA testing, and should be considered for prophylactic antiviral therapy. Monitoring and prophylaxis should continue at least 6 months following completion of therapy. Patients with evidence of reactivation of hepatitis B should immediately discontinue obinutuzumab and ibrutinib and be treated for hepatitis B in conjunction with appropriate specialists.

8.1.15 COVID-19 Vaccine

Patients are encouraged to receive COVID 19 vaccination. Vaccination status will not interfere with trial participation.

8.2 Dose Modifications

AERS reporting may be required for some adverse events (See Section 9.0)

8.2.1 Dose Modifications for Hematologic Toxicity

Dose modifications should be made based on day 1 values for each cycle, or the presence of significant bleeding or febrile neutropenia. Hematologic toxicity for the purpose of dose modifications will be graded according to 2018 IWCLL criteria[16], which account for pretreatment cytopenias. These are graded as follows:

Grade	Decrease in Platelets* or Hgb** from pretreatment value	Absolute Neutrophil Count (ANC) (uL)***
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-74%	≥500 and <1000
4	≥75%	<500

* Platelet counts must be below normal levels for any grade toxicity to be recorded. If platelet count is $<20x10^{12}$/L, this will be considered grade 4 toxicity.

**Hgb levels must be below normal levels for any grade toxicity to be recorded.

***If ANC is <1000 prior to study, the patient is not evaluable for toxicity assessment based on ANC.

Dose Level	Ibrutinib	Venetoclax	Obinutuzumab
1 (starting dose)	420 mg	400 mg	1000 mg
-1	280 mg	300 mg	No obinutuzumab
-2	140 mg	200 mg	No obinutuzumab
-3	No ibrutinib	100 mg	No obinutuzumab
-4	No ibrutinib	No venetoclax	No obinutuzumab

- For grade 3 or 4 hematologic toxicity, significant bleeding, or febrile neutropenia, the treating investigator should attempt to assign causality to one or more agents. This may be done in conjunction with the Alliance Study Chair if desired. Grade 3 neutropenia does not require dose interruption or modification unless accompanied by fever, and lymphopenia/lymphocytosis do not require dose modification or interruption. Grade 3 or higher hypertension does not require dose interruption or modification if blood pressure is managed medically. For other grade 3/4 hematologic toxicities, the causative agent(s) should be held until toxicity returns to ≤ grade 1 (or baseline), while other drugs should remain at original doses and schedule. All drugs should be held if causality is unable to be attributed to an individual or group of agents. For the first occurrence, drug may be restarted at the original dose. For the second occurrence and beyond, dose reduce by 1 level. If all three drugs were held then all three drugs need to be dose reduced. Consider the use of intermittent growth factor for grade 3 or 4 neutropenia.
- Drugs may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, the offending drug must be discontinued permanently. There is no time limit to hold drugs for unrelated toxicity in the absence of progressive disease.
- Patients who are dose-reduced and are stable for 3 cycles may have dose escalated 1 level each cycle.
- Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes

(e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

- A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored by the treating physician. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of symptoms, and can then be restarted.

8.2.2 Dose Modifications for Non-Hematologic Toxicity

Dose Level	Ibrutinib	Venetoclax	Obinutuzumab
1 (starting dose)	420 mg	400 mg	1000 mg
-1	280 mg	300 mg	No obinutuzumab
-2	140 mg	200 mg	No obinutuzumab
-3	No ibrutinib	100 mg	No obinutuzumab
-4	No ibrutinib	No venetoclax	No obinutuzumab

- For grade 3 or 4 non-hematologic toxicity at possibly, probably, or definitely related to an individual agent, hold that agent until toxicity returns to ≤ grade 1 (or baseline). For a first occurrence, drug may be restarted at the same dose. For a second occurrence, once toxicity resolves, dose reduce by 1 dose level. Prior to dose reduction for diarrhea, aggressive supportive care should be instituted. All drugs should be held if causality is unable to be attributed to an individual or group of agents.
- Drug may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, the offending drug must be discontinued permanently. There is no time limit to hold drugs for unrelated toxicity in the absence of progressive disease.
- Aspergillus infection has been reported in patients taking ibrutinib. Any patient diagnosed with aspergillus or other disseminated fungal infection should have ibrutinib withheld until fungal infection is resolved and preferably until antifungal therapy is complete.
- For infusion reactions attributable to obinutuzumab, supportive care should be provided per institutional protocols. Obinutuzumab can be continued without dose modification. However, at the discretion of the treating physician and with study chair approval, obinutuzumab can be discontinued for severe infusion reactions.
- Obinutuzumab should be discontinued in the case of progressive multifocal leukoencephalopathy (PML) or development of hepatitis B reactivation.
- For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of non-warfarin anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.
- Ibrutinib is metabolized in the liver. Please see the Child-Pugh scoring system outlined in Appendix I to determine whether dose modifications are warranted according to the following instructions. For patients who develop mild liver

impairment while on study (Child-Pugh class A), the recommended dose is 140 mg daily (two capsules). For patients who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose is 70 mg daily (one capsule). Patients who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and may be re-treated according to resolved hepatic conditions (i.e., 140 mg or 280 mg for moderate or mild impairment, respectively). Monitor patients for signs of toxicity and follow dose modification guidance as needed.

- For any Grade 2 toxicity that is causing significant discomfort or functional impairment, dose interruption and modifications may be made using the same guidelines as for Grades 3 and 4 at the discretion of the treating physician ONLY AFTER discussion with the study chair.
- For blood chemistry changes or symptoms suggestive of TLS:
  - Withhold the next day's dose. If it resolves within 24-48 hours of last dose, resume at the same dose.
  - For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose.
  - For any events of clinical TLS, resume at a reduced dose following resolution.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. For the specific AE of tumor lysis syndrome, grading will be performed both according to CTCAE criteria and Howard criteria, where the TLS will also be categorized as laboratory or clinical. Howard criteria can be found in Appendix II. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Hypertension	Vascular disorders
Atrial fibrillation	Cardiac disorders

Infections (grade 3-5 only)	Infections and infestations
Platelet count decreased	Investigations
Rash maculopapular	Skin and subcutaneous tissue disorders
Arthralgia	Musculoskeletal and connective tissue disorders
Edema limbs	General disorders and administration site conditions
Bruising	Injury, poisoning and procedural complications
Tumor lysis syndrome	Metabolism and nutrition disorders
Fatigue	General Disorders and administration site conditions
Diarrhea	Gastrointestinal disorders

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols* > *Documents*> *Protocol Related Documents*> *Adverse Event Reporting*; and
- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (RAVE-CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

- Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

9.3.2 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A041702 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

≤ Grade 4 anemia, neutropenia, thrombocytopenia, and hospitalization resulting from these do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

New primary malignancies should be reported using Medidata Rave.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Secondary Malignancy:

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlines in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting unless otherwise specified.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization

or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at http://ctep.cancer.gov/). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ibrutinib (PCI-32765, NSC 748645)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2086 patients.* Below is the CAEPR for Ibrutinib (PCI-32765).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.9, April 10, 2025[1]

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (leukostasis)[2]	
		Leukocytosis[2]	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Ventricular arrhythmia	
		Ventricular fibrillation	

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Ventricular tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		***Fatigue (Gr 3)***
Fever			
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (drug-induced liver injury)	
		Hepatobiliary disorders - Other (hepatotoxicity)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
		Hepatitis B reactivation	
	Infection[3]		***Infection[3] (Gr 3)***
		Infections and infestations - Other (bronchopulmonary and central nervous system infections)[4]	
		Infections and infestations - Other (hepatitis E)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Lymphocyte count increased[2]		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
White blood cell decreased			
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
		Hyperuricemia	
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Bone pain			
	Muscle cramp		
	Myalgia		

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin)[5]		
		Treatment related secondary malignancy[5]	
NERVOUS SYSTEM DISORDERS			
	Headache		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
		Stroke	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
		Pneumonitis[6]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Purpura		
		Skin and subcutaneous tissue disorders - Other (angioedema)[7]	
	Skin and subcutaneous tissue disorders - Other (rash)[8]		***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (neutrophilic dermatosis)	
		Skin and subcutaneous tissue disorders - Other (panniculitis)	
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
		Vascular disorders - Other (cutaneous vasculitis)	
	Vascular disorders - Other (hemorrhage)[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Leukostasis and/or leukocytosis have been observed especially in patients with chronic lymphocytic leukemia (CLL) and mantle cell leukemia (MCL).

[3]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Fungal infections especially respiratory tract infections due to aspergillus and/or pneumocystis and central nervous system (CNS) infections due to aspergillus have been observed in clinical trials of ibrutinib. These reports may include incidents of presumptive fungal infections based on response to anti-fungal agents and/or radiographic evidence.

[5]Other malignant diseases have been observed in patients who have been treated with ibrutinib including solid tumors, skin cancer, and hematological malignancies.

[6]Pneumonitis is included in the group term Interstitial Lung Disease (ILD) which also includes lung infiltration, bronchiolitis, pulmonary fibrosis, eosinophilc pneumonia, pulmonary toxicity, and alveolitis allergic.

[7]Angioedema may be seen in association with the immune-related adverse event of anaphylaxis.

[8]Rash may include but is not limited to the terms dermatitis, erythema, rash generalized, rash maculo-papular, rash pustular, rash pruritic, and urticaria.

[9]It is possible that treatment with ibrutinib may increase the risk of hemorrhage which may occur anywhere in the body including CNS hemorrhage (including but not limited to Intracranial hemorrhage, Intraventricular hemorrhage, and Subdural hematoma), Ecchymoses, Purpura (petechia), Eye disorders - Other (eye hemorrhage), Eye disorders - Other (retinal hemorrhage), Gastrointestinal hemorrhage (including but not limited to Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage), Genitourinary tract hemorrhage (including but not limited to Hematuria and Vaginal hemorrhage), Respiratory tract hemorrhage (including but not limited to Epistaxis), and Spontaneous hemorrhage.

Adverse events reported on Ibrutinib (PCI-32765) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ibrutinib (PCI-32765) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemorrhagic diathesis); Blood and lymphatic system disorders - Other (lymphadenitis); Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye pain; Floaters; Glaucoma; Keratitis; Periorbital edema; Photophobia; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Cheilitis; Colitis; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gluteal intramuscular bleed); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Oral dysesthesia; Oral pain; Pancreatitis; Periodontal disease; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Generalized edema; Injection site reaction; Localized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion-related reaction; Injury, poisoning and procedural complications - Other (excoriation)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (cardiac murmur); Investigations - Other (CRP increased); Lymphocyte count decreased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia;

Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (lactose intolerance)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Flank pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (muscle rigidity); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dizziness; Dysgeusia; Encephalopathy; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (mental impairment); Nervous system disorders - Other (PML); Nervous system disorders - Other (parosmia); Paresthesia; Reversible posterior leukoencephalopathy syndrome; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Insomnia; Restlessness
RENAL AND URINARY DISORDERS - Cystitis noninfective; Renal and urinary disorders - Other (calculus bladder); Renal and urinary disorders - Other (polyuria); Urine discoloration; Urinary frequency; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dyspareunia; Reproductive system and breast disorders - Other (hematospermia); Vaginal dryness
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Hiccups; Laryngeal inflammation; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (alveolitis allergic); Respiratory, thoracic and mediastinal disorders - Other (nasal ulcer); Sinus disorder; Sinus pain; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail discoloration; Nail loss; Photosensitivity; Pruritus; Skin atrophy; Skin hyperpigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hot flashes; Thromboembolic event; Vascular disorders - Other (peripheral coldness)

Note: Ibrutinib (PCI-32765) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Obinutuzumab (NSC 793436)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1387 patients.* Below is the CAEPR for Obinutuzumab (NSC 793436).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, January 15, 2025[1]

Adverse Events with Possible Relationship to Obinutuzumab (Gazyva) (CTCAE 5.0 Term) [n= 1387]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	

Adverse Events with Possible Relationship to Obinutuzumab (Gazyva) (CTCAE 5.0 Term) [n= 1387]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
Blood and lymphatic system disorders - Other (B-cell depletion)[2]			***Blood and lymphatic system disorders - Other (B-cell depletion)[2] (Gr 2)***
		Disseminated intravascular coagulation	
CARDIAC DISORDERS			
		Atrial fibrillation[3]	
		Cardiac disorders - Other (tachyarrhythmia)[3]	
		Chest pain - cardiac[3]	
		Heart failure[3]	
		Myocardial infarction[3]	
		Paroxysmal atrial tachycardia[3]	
		Sinus tachycardia[3]	
		Supraventricular tachycardia[3]	
		Ventricular tachycardia[3]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Gastrointestinal perforation[4]		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[5]		***Chills[5] (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever[5]			***Fever[5] (Gr 2)***
	Non-cardiac chest pain		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis[6]	
		Cytokine release syndrome	
		Serum sickness[6]	
INFECTIONS AND INFESTATIONS			
		Hepatitis B reactivation[7]	
	Infection[7]		***Infection[7] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Infusion related reaction[5]			***Infusion related reaction[5] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased[8]			***Neutrophil count decreased (Gr 2)***

Adverse Events with Possible Relationship to Obinutuzumab (Gazyva) (CTCAE 5.0 Term) [n= 1387]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Hyperuricemia		***Hyperuricemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (basal cell carcinoma)	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma of skin)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy [PML])	
RENAL AND URINARY DISORDERS			
	Dysuria		
	Urinary incontinence		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea[5]		***Dyspnea[5] (Gr 2)***
	Rhinorrhea		***Rhinorrhea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Flushing[5]		***Flushing[5] (Gr 2)***
	Hypertension[5]		***Hypertension[5] (Gr 2)***
	Hypotension[5]		***Hypotension[5] (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] B-cell lysis and depletion are considered to be the primary mechanism of action of obinutuzumab.

[3]These events are considered expected in the context of worsening an already existing cardiac condition, such as heart failure, cardiac ischemia and arrhythmia (atrial fibrillation or atrial flutter).

[4]Gastrointestinal perforation may occur in Gastrointestinal lymphomas and may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infusion related reactions, including high-grade hypersensitivity reactions, may occur during or immediately after administration of obinutuzumab; clinical manifestations may include as, fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing (dyspnea), bronchospasm and hypoxia.

[6]Anaphylaxis (immediate-onset hypersensitivity) with symptoms including dyspnea, bronchospasm, hypotension, urticaria, and tachycardia as well as late-onset hypersensitivity (serum sickness) with symptoms including chest pain, diffuse arthralgia, and fever, which may be life-threatening have been observed in obinutuzumab trials.

[7]Infection may include viral, bacterial and fungal infections in any organ system under the INFECTIONS AND INFESTATIONS SOC.

[8]Neutrophil count decreased (neutropenia) may be of late onset, prolonged, and in rare cases, life threatening or fatal.

Adverse events reported on Obinutuzumab (Gazyva) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Obinutuzumab (Gazyva) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
GASTROINTESTINAL DISORDERS - Dyspepsia; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Flu like symptoms; Malaise
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall
INVESTIGATIONS - Blood lactate dehydrogenase increased
METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypokalemia; Metabolism and nutrition disorders - Other (vitamin D deficiency)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (neuropathy peripheral); Paresthesia; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hiccups; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis

Note: Obinutuzumab (Gazyva) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Venetoclax (ABT-199, NSC 766270)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 4751 patients. Below is the CAEPR for Venetoclax (ABT-199).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, July 22, 2025[1]

Adverse Events with Possible Relationship to Venetoclax (ABT-199) (CTCAE 5.0 Term) [n= 4751]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (drug-induced liver injury)	
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Hyperphosphatemia		
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Venetoclax (ABT-199) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Venetoclax (ABT-199) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (coronary artery disease); Heart failure; Myocardial infarction; Sinus tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
EYE DISORDERS - Cataract
GASTROINTESTINAL DISORDERS - Abdominal pain; Belching; Colitis; Dry mouth; Dyspepsia; Dysphagia; Esophageal pain; Esophageal ulcer; Gastrointestinal disorders - Other (Crohn's disease); Mucositis oral; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Flu-like symptoms; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); Injection site reaction; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal)
IMMUNE SYSTEM DISORDERS - Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Infusion-related reaction; Injury, poisoning and procedural complications - Other (laceration)
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypervolemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acute myeloid leukemia); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Richter's syndrome); Treatment-related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Intracranial hemorrhage; Ischemia cerebrovascular; Nervous system disorders - Other (neuropathy peripheral); Peripheral sensory neuropathy; Syncope
PSYCHIATRIC DISORDERS - Confusion; Delirium; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Ovarian rupture
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pneumonitis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asphyxia)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Pruritus; Rash acneiform; Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Venetoclax (ABT-199) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.5 Adverse Events of Special Interest

Non drug Specific AESIs (applicable to all Roche / GNE studies):

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin) - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

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

AESIs specific to Venclexta (Venetoclax):

- Tumor lysis syndrome (irrespective of seriousness)

AESIs specific to Gazyva (Obinutuzumab):

- Tumor lysis syndrome (irrespective of seriousness)
- Second Malignancy

10.0 DRUG INFORMATION

10.1 General Considerations:

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

10.1.1 Contraception

Men must use a barrier method while on treatment with obinutuzumab and for 180 days after the last dose of obinutuzumab.

Women taking obinutuzumab must be advised to use contraceptives for 18 months after obinutuzumab treatment.

10.2 Ibrutinib (NSC 748645, IND [redacted] IND holder CTEP/DCTD/NCI)

Investigators ordering and/or dispending supplied agents at any time for study treatment must be concurrently registered with PMB, DCTD, and NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents. See Section 10.5 for agent ordering, agent accountability, agent inventory records, investigator brochure availability, and useful links and contacts information for all NCI-supplied agents

Procurement and Availability

Ibrutinib is supplied by Pharmacyclics, Inc., and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Do not use commercial supply.

Formulation

Ibrutinib is supplied as hard gelatin capsules containing micronized ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are manufactured as 140mg in a size 0, gray, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 or 120 capsules. Ibrutinib capsules are to be dispensed in their original containers.

Storage

The recommended storage condition for ibrutinib capsules is 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F).

Stability

Shelf life surveillance of the intact bottles is ongoing.

Administration

Orally, with 8 ounces (approximately 240ml) of water. The capsules are to be swallowed intact. Doses are to be taken at about the same time each day. If a dose is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose.

Drug Interactions

Ibrutinib is primarily metabolized by CYP3A4. Grapefruit and Seville orange juices should be avoided.

Adverse Events

For a comprehensive adverse events and potential risks list (CAEPR), please see Section 9.4.1.

10.3 Obinutuzumab (NSC 793436, IND [redacted] IND holder CTEP/DCTD/NCI)

Investigators ordering and/or dispending supplied agents at any time for study treatment must be concurrently registered with PMB, DCTD, and NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents. See Section 10.5 for agent ordering, agent accountability, agent inventory records, investigator brochure availability, and useful links and contacts information for all NCI-supplied agents

Procurement and Availability

Obinutuzumab is supplied by Genentech, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Do not use commercial supply.

Formulation

Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and highly purified water (HPW). HPW meets the specified limits for water for injections (WFI) according to USP.

Storage

2°C and 8°C, protected from light. If a storage temperature excursion is identified, promptly return obinutuzumab to 2°C - 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability for use.

Stability

For microbiological stability, the diluted GAZYVA infusion solution should be used immediately. Dilute under appropriate aseptic conditions. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours followed by 48 hours at room temperature (total prepared infusion stability of 72 hours). Please note that the product does not contain preservatives and safeguards should be in place to prevent microbial contamination if the product is not used immediately.

Preparation

Dilute into a 250 mL 0.9% sodium chloride PVC or non- PVC polyolefin infusion bag. Obinutuzumab can be 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. Do not shake or freeze. Institutional methods of preparation are acceptable, including diluting the first dose in 100ml NS.

Administration

Intravenous infusion

Chronic Lymphocytic Leukemia

Loading dose (Cycle 1 only), 100 mg infused at 25 mg/hr with no increase in infusion rate. The 100 mg dose of obinutuzumab given on Day 1 of Cycle 1 can also be administered in 100 mL NS.

Day 2 (Cycle 1 only) – dose should be started at 50 mg/hr and can be increased in increments of 50 mg/hr every 30 minutes to maximum infusion rate of 400 mg/hr

Subsequent infusions – if no infusion reaction with previous infusion and final infusion rate > 100 mg/hr, then all subsequent infusions can start at 100 mg/hr and increase every 30 minutes to maximum of 400 mg/hr

Drug Interactions

No formal drug-drug interaction studies have been performed, although limited drug interaction sub-studies have been undertaken for obinutuzumab with bendamustine,

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and FC (fludarabine, cyclophosphamide) and chlorambucil. Co-administration with obinutuzumab had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP; in addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of obinutuzumab. A risk for interactions with concomitantly used medicinal products cannot be excluded.

Adverse Events

For a comprehensive adverse events and potential risks list (CAEPR), please see Section 9.4.2.

10.4 Venetoclax (NSC 766270, IND [redacted] IND holder CTEP/DTCD/NCI)

Investigators ordering and/or dispending supplied agents at any time for study treatment must be concurrently registered with PMB, DCTD, and NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents. See Section 10.5 for agent ordering, agent accountability, agent inventory records, investigator brochure availability, and useful links and contacts information for all NCI-supplied agents

Procurement and Availability

Venetoclax is supplied by Abbvie/Genentech, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Do not use commercial supply.

Formulation

Venetoclax tablets are supplied as oblong, bi-convex pale yellow or beige tablets that contain 10 mg, 50 mg or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium

dioxide. Each tablet is debossed with "V" on one side and a "10", "50" or "100" corresponding to the tablet strength on the other side.

The 10 mg and 50 mg supplies will be provided in blister cards. Each 10 mg blister card will contain 16 tablets, while each 50 mg blister card will contain 8 tablets. The 100 mg tablets will be supplied in 32 count bottles.

Storage

Store between 15° to 30°C (59° to 86°F).

If a storage temperature excursion is identified, promptly return venetoclax to between 15° to 25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability

Stability studies are ongoing.

Administration

Tablets should be taken orally once daily, at approximately the same time, with a meal and water. Do not chew, crush, or break tablets.

If a dose is missed by less than 8 hours, take the missed dose right away and take the next dose as usual. If a dose is missed by more than 8 hours, the patient should wait and take the next dose at the usual time.

Patients should not take an additional dose if they vomit after taking venetoclax. They should take the next dose at the usual time the following day.

Drug Interactions

Venetoclax is predominantly metabolized by CYP3A4/5. Concomitant use of venetoclax with strong inhibitors of CYP3A at initiation and during ramp-up phase is contraindicated. For patients who have completed the ramp-up phase and are on a steady daily dose, reduce the dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor

Avoid concomitant use of moderate CYP3A inhibitors or P-gp inhibitors. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the dose by at least 50%. Resume the 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.

Avoid concomitant use with strong CYP3A inducers or moderate CYP3A inducers.

Venetoclax may cause a significant increase in Cmax and AUC of warfarin. International normalized ratio (INR) should be monitored closely in patients receiving warfarin.

Venetoclax had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability.

Avoid grapefruit products, Seville oranges, and starfruit during treatment

Adverse Events

For a comprehensive adverse events and potential risks list (CAEPR), please see Section 9.4.3.

10.5 NCI-supplied Agent Ordering, Accountability, Inventory, IB Availability, and Contacts

Investigators ordering and/or dispending supplied agents at any time for study treatment must be concurrently registered with PMB, DCTD, and NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, and a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

1. CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
2. NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
3. PMB Online Agent Order Processing (OAOP) Application: https://ctepcore.nci.nih.gov/OAOP/pages/login.jspx
4. PMB Policies and Guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
5. CTEP Identity and Access Management (IAM) Account: https://ctepcore.nci.nih.gov/iam/
6. CTEP Associate Registration and IAM Account Help: ctepreghelp@ctep.nci.nih.gov
7. IB Coordinator: IBCoordinator@mail.nih.gov

8. PMB Email: PMBAfterHours@mail.nih.gov

PMB Phone and Hours of Service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

11.0 MEASUREMENT OF EFFECT

Criteria for response will utilize the Revised 2018 IWCLL [16] for response which includes clinical, hematologic, and bone marrow features as derived from the initial 1996 guidelines[21].

There are 8 possible response categories: complete response (CR), CR with incomplete recovery (CRi), clinical CR (CCR), nodular partial response (nPR), partial response (PR), PR with persistent lymphocytosis (PRL), stable disease (SD), and progressive disease (PD). Once a CR/CRi/CCR is achieved, response cannot worsen and be recorded as nPR/PR/PRL/SD at a subsequent assessment; likewise, once nPR/PR/PRL is achieved, response cannot worsen and be recorded as SD at a subsequent assessment. The criteria for each response category are described in detail below.

11.1 Complete response

Requires all of the following on response evaluation testing and then clinical stability for a period of at least two months:

- Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan;
- No hepatomegaly or splenomegaly on physical exam
- No clonal B-cells in the blood by flow cytometry;
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1,500/µL, platelets > 100,000/µL, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count < 5,000/µL;

Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, patients should be considered to be a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells, it should be considered a partial response. If the marrow is hypocellular a bone marrow should be performed in 2-3 months. If blood counts (polymorphonuclear leukocytes < 1,500/µL, platelets < 100,000/µL) fail to recover at the time of the response evaluation but there is otherwise no evidence of CLL otherwise, a repeat determination should be performed at the time of count recovery (polymorphonuclear leukocytes ≥ 1,500/µL, platelets > 100,000/µL) but should not exceed 6 months.

CR should continue to be reported as CR at each subsequent clinical assessment until documentation of PD.

11.2 Complete response with incomplete recovery (CRi)

- Patients who fulfill the criteria for CR with the exception of a persistent cytopenia (CR with incomplete recovery, CRi) that is believed to be treatment related will be considered a CRi. As stated above, patients falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at this time reveals no CLL, these patients will be considered to be in complete remission at that time.
- A CRi assessment can continue to be reported as CRi or improve to CR at a subsequent clinical assessment, until documentation of PD.

11.3 Clinical CR (CCR)

- Patients who fulfill the criteria of CR with exception of not having a bone marrow biopsy performed will be considered a clinical CR.
- A CCR assessment can continue to be reported as CCR, be recorded as CRi, or improve to CR at a subsequent clinical assessment, until documentation of PD.

11.4 Nodular PR (nPR)

- Patients who fulfill the criteria of CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR).
- A nPR assessment can continue to be reported as nPR or improve to CR/CRi/CCR/CRi at a subsequent clinical assessment, until documentation of PD.

11.5 Partial Response

Requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value (in those patients with lymphocytosis pre-treatment), ≥ 50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly/hepatomegaly by physical exam on response evaluation testing and then clinical stability for a period of at least two months. Additionally, these patients must have one of the following:

- Polymorphonuclear leukocytes ≥ 1,500/µL or 50% improvement from pre-treatment value
- Platelets > 100,000/µL or 50% improvement from pre-treatment value
- Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pre-treatment value
    - A PR assessment can continue to be reported as PR or improve to CR/CRi/CCR/nPR at a subsequent clinical assessment, until documentation of PD

11.6 Partial response except persistent lymphocytosis (PRL)

Patients who meet the criteria for PR with the exception of having less than a 50% reduction in peripheral lymphocyte count will be considered a partial response except persistent lymphocytosis (PR-L). These patients should continue to be followed on therapy and response status updated if the lymphocyte count does decrease by ≥ 50%.

A PRL assessment can continue to be reported as PRL or improve to CR/CRi/CCR/nPR/PR at a subsequent clinical assessment, until documentation of PD.

11.7 Progressive Disease (PD)

Because of the well-described lymphocytosis that occurs with ibrutinib, patients receiving ibrutinib will not be considered to have progressive disease if they have an increase in lymphocyte count without other disease related symptoms (increasing lymph nodes, splenomegaly, disease-associated constitutional symptoms) (See Section 8.2 for more information). Progressive disease will be characterized by any one of the following events:

- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter (in patients on Arm 1, or those on Arms 2 or 3 who are not receiving ibrutinib)
- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm), appearance of new palpable lymph nodes

- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin, appearance of palpable hepatomegaly or splenomegaly which was not previously present
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes)
- The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels >2 g/dL or to < 10 g/dL, or by a decrease of platelet counts > 50% or to < 100,000/µL, which occurs at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.

11.8 Stable Disease

Patients who do not fulfill the criteria for complete or partial response as defined above (CR, CRR, CRi, nPR, PR, PR-L) but do not exhibit progressive disease will be considered to have stable disease.

A SD assessment can continue to be reported as SD or improve to CR/CRi/CCR/nPR/PR/PRL at a subsequent clinical assessment, until documentation of PD.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.1.1 Cycle 1 through Cycle 15 Day 28

Arm 1: Continue obinutuzumab through cycle 6 and ibrutinib until the end of Cycle 15. Patients who complete 14 cycles of protocol therapy will undergo Day 1 of Cycle 15 response assessment and staging. During this time, all patients will complete Cycle 15 of ibrutinib therapy. All patients will then continue with ibrutinib maintenance until disease progression as described in Section 12.1.2.

Arm 2: Continue obinutuzumab through Cycle 6, and ibrutinib and venetoclax until the end of Cycle 14. Patients who complete 14 cycles of protocol therapy will undergo Day 1 of Cycle 15 response assessment, central BM MRD and staging per Section 5.0 and 6.2. During this time, all patients will complete Cycle 15 of ibrutinib therapy.

- Patients who are determined to have BM MRD+ (performed centrally) disease will continue ibrutinib maintenance until disease progression as described in Section 12.1.2.
- Patients who are determined to have BM MRD- (performed centrally) disease but without CR (determined locally) will continue ibrutinib maintenance therapy until disease progression as described in Section 12.1.2.
- Patients who are BM MRD- and with CR will be continue to Observation until disease progression as described in Section 12.1.2.

12.1.2 After Cycle 15 Day 28

Ibrutinib: Continue ibrutinib until disease progression, with patients followed every 3 cycles for 6 years from registration (Step 1) and every 6 cycles thereafter until progression. See Section 5.0.

Observation: Patients who go on to observation will be followed per Section 5.0 every 3 cycles for 6 years from registration (Step 1) and every 6 cycles thereafter until disease progression.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (if applicable)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients who are treated according to the scheduled protocol therapy (as described in Section 7.0) will follow the study calendar outlined in Section 5.0. After documented progression of CLL (at any stage, on any arm), patients will go on to survival follow up, followed every 6 months until 10 years from Step 1 registration.

12.3.2 Follow-up for Patients Who Stop Study Treatment Early

Patients who stop due to toxicity at any point during therapy will go to clinical follow up (see column in Section 5.0), until disease progression. At that time, patients go to survival follow up, followed every 6 months until 10 years from registration (Step 1).

Patients who receive non-protocol CLL-directed therapy will go to clinical follow up (as outlined in Section 5.0) until disease progression. At that time, patients go to survival follow up (see Data Submission Schedule on A041702 Alliance and CTSU study page), followed every 6 months until 10 years from registration (Step 1).

Patients who stop study treatment early to receive a non-protocol therapy unrelated to their CLL diagnosis will go to clinical follow up (as outlined in Section 5.0), until disease progression. At that time, patients go to survival follow up, followed every 6 months until 10 years from registration (Step 1).

Follow up for patients who withdraw prior to starting any protocol treatment (with or without progression) will go to survival follow up, followed every 6 months for up to 10 years from registration (Step1).

12.3.2 Follow-up for Specimen Submission

Specimen submission must continue during all treatment stages, observation and clinical follow-up. Specimen submission are not required if patient is in survival follow-up.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study design

This is a randomized, open label, multi-center phase III trial designed to evaluate whether the treatment strategy of ibrutinib/venetoclax/obinutuzumab (IVO) followed by ibrutinib maintenance (IM) for patients without BM MRD- CR and IM discontinuation for patients with BM MRD- CR improves progression-free survival (PFS) over ibrutinib/obinutuzumab (IO) followed by IM in previously untreated, older (age ≥ 65 years) CLL patients who are symptomatic and require therapy by the IWCLL guidelines. This trial implements a group

sequential design with two interim analyses for superiority and three interim analyses for futility using the O'Brien-Fleming version of the Lan Demets alpha-spending and beta-spending functions, respectively, to control the type I and II error rates. The sample size calculation was conducted using EAST version 6.4 software (Cytel Inc.).

13.2 Statistical design and analysis for the primary endpoint

13.2.1 Primary endpoint

The primary endpoint in this phase III trial is progression-free survival (PFS), which will be defined from randomization date until the earlier of disease progression or death from any cause, censoring patients alive and progression-free at the date of last known clinical assessment. If a patient begins a subsequent, non-protocol CLL therapy, we will collect reason for beginning subsequent treatment. If the reason for beginning a non-protocol CLL treatment prior to a documented progression is due to symptomatic disease or clinical deterioration, then this will be considered an event for PFS at the last assessment date prior to start of non-protocol therapy. Alternatively, if the reason for beginning a non-protocol CLL treatment prior to a documented progression is due to some other reason (e.g., experiences an adverse event and chooses to begin a different therapy), clinical data will be carefully reviewed on a case-by-case basis and it will be determined whether to treat as an event for PFS or censor at the last assessment date prior to start of non-protocol therapy. Using an intent-to-treat approach, all randomized patients will be included in the analysis of the primary endpoint in the arm to which they were randomized.

13.2.2 Statistical design

Patients will be randomized using dynamic allocation procedures in a 1:1 manner to the two treatment arms: IO vs. IVO. Randomization will be stratified on Rai stage (intermediate vs. high) and high-risk FISH abnormality del(17p13.1) (present vs. absent).

The primary goal of this phase III trial is to determine whether the experimental treatment strategy of IVO followed by IM for patients without BM MRD- CR and IM discontinuation for patients with BM MRD- CR has superior PFS compared to the control treatment strategy of IO followed by IM for all patients. We will test the null hypothesis that the hazard ratio is equal to 1.0 versus the alternative hypothesis that the hazard ratio is equal to 0.55 in favor of the experimental treatment strategy. Assuming exponential parameters for control and experimental treatment strategy groups are 0.071 and 0.039, respectively, this corresponds to a median PFS of 9.717 years vs. 17.667 years and is equivalent to 5-year PFS rates of 70% vs. 82.187%. Based on design assumptions, the 70% PFS rate at 5 years assumed for the control treatment strategy group corresponds with data available from a randomized phase III trial, in which previously untreated patients aged 65 years or older received ibrutinib until disease progression or unacceptable toxic effects and had a PFS estimate at 18 months of 90%.[2]

There is 90% power for this one-sided log-rank test of superiority with the experimental treatment strategy versus the control treatment strategy using a group sequential design and constraining the one-sided type I error to 0.025 (i.e., two-sided error of 0.05). This design requires 128 events and translates to 431 total evaluable patients when assuming uniform accrual over 3 years and a minimum follow-up of 5 years.

This design includes two interim analyses for superiority when 50% and 75% of the expected number of events have been observed and three interim analyses for futility when 25%, 50%, and 75% of the expected number of events have been observed. Decision rules for interim and final analyses were determined using the O'Brien-Fleming version of the Lan Demets alpha-spending and beta-spending functions.

13.2.3 Analysis plan

The primary endpoint of PFS will be compared between the experimental and control treatment strategy groups using a stratified log-rank test (stratified on Rai stage, intermediate vs. high, and del(17p13.1) by FISH, present vs. absent). The Kaplan-Meier method will be used to estimate PFS distributions. Five-year PFS estimates, medians, and corresponding hazard ratios will be provided with 95% confidence intervals for each treatment strategy. All patents randomized to a treatment arm will be included in the analysis of the primary endpoint.

13.2.4 Interim analysis decision rules

For the primary comparison of PFS between experimental and control treatment strategies, there will be three interim evaluations. The first planned interim analysis will occur after approximately 25% of the expected number of events have been observed. This is equivalent to 32 events and is anticipated shortly prior to year 3 of the study. After that, two more interim evaluations are planned after approximately 50% and 75% of the expected number of events are observed. All interim evaluations will include an assessment of futility to identify if there is strong evidence of worse outcome with the experimental treatment strategy (per criteria outlined below). If at any of the planned interim analyses the futility boundary is crossed, then the Alliance DSMB will determine whether accrual should be suspended, treatment modified, or trial terminated based upon review of the data. Only the second and third interim evaluations will include an assessment of superiority to avoid stopping the trial too early without adequate follow-up of patients who discontinue IM as part of the experimental treatment strategy. If, at these planned interim analyses, the superiority boundary is crossed (per criteria outlined below), then the Alliance DSMB will determine whether the trial can be stopped with early release of results based upon review of the data. For all interim analyses, the z-statistic from the one-sided stratified log-rank test will be compared to the boundary values determined by the trial design. The interim analysis boundaries and characteristics were generated using EAST version 6.4 software (Cytel Inc.).

13.2.5 Final analysis decision rules

The final analysis comparing PFS between experimental and control treatment strategies is to be conducted after 128 events are observed or all patients are followed for at least 5 years (whichever occurs first). This analysis of PFS will be conducted using the remaining alpha and beta following the interim analyses where the overall one sided alpha level is 0.025 and the overall beta level is 0.10. If at the final analysis the z-statistic from the one-sided stratified log-rank test is less than -2.014 and in favor of the experimental treatment strategy group, then the experimental treatment strategy will be declared a success; otherwise the control treatment strategy will be preferred in this patient population. The final analysis boundaries and characteristics were generated using EAST version 6.4 software (Cytel Inc.).

Boundary rules for comparison of PFS between experimental and control treatment strategies

Information Fraction	Cumulative Events	Cumulative Alpha spent	Cumulative Beta spent	Superiority Boundary Z (HR)	Futility Boundary Z (HR)	Estimated Analysis Time (Yrs)
0.25	32	0	0.00095	NA	1.415 (1.649)	2.9
0.50	64	0.00153	0.01942	-2.963 (0.477)	-0.319 (0.923)	4.4

0.75	96	0.00965	0.05632	-2.359 (0.618)	-1.289 (0.769)	6.1
1.0	128	0.025	0.09837	-2.014 (0.700)	-2.014 (0.700)	8.0

Boundaries use the O'Brien Fleming version of the Lan-Demets stopping rules. The superiority boundary rule is not applicable (NA) at the first interim analysis and the incremental crossing probability at each subsequent analysis under the alternative hypothesis is 0.284, 0.434, and 0.183, respectively. The incremental futility crossing probability at each analysis under the null hypothesis is 0.078, 0.548, 0.279, and 0.072, respectively. The futility boundaries are not binding.

13.3 Sample size, accrual time, and study duration

13.3.1 Sample size

The statistical design is fully described in Section 13.2. The study design requires 431 total evaluable patients (n ≈ 215 randomized to each arm). With 5% overaccrual to account for ineligibilities, cancellations, and major violations, the target accrual is 454 patients.

13.3.2 Accrual rate and accrual duration

From cooperative group trial A041202, a phase III trial that enrolled previously untreated CLL patients aged 65 years or older, the screening rate was 22 patients per month and the accrual rate was 18 patients per month. For A041702, a successor study which will enroll previously untreated CLL patients aged 65 years or older, we estimate lower screening and accrual rates of 15 and 13 patients per month, respectively, over 3 years. If there are no major issues of patient safety and the study does not stop early at the time of interim analyses, the maximum expected study duration is 8 years when all patients have been followed a minimum of approximately 5 years.

13.3.3 Primary endpoint completion date for ClinicalTrials.gov reporting

For the purpose of ClinicalTrail.gov reporting, the primary endpoint completion date (PECD) for this study is approximately 5 years after the randomization of the last patient.

13.4 Supplementary analysis plans

With the exception of toxicity and tolerability measures, which will be limited to patients who begin treatment on either arm, analyses will include all randomized patients.

In a sensitivity analysis of the primary endpoint, PFS will be defined from randomization date until the earlier of disease progression or death from any cause, censoring patients alive and progression-free at the date of last known clinical assessment, without taking into consideration the start of non-protocol CLL therapy. PFS using this modified definition will be compared between the experimental and control treatment strategy groups using a stratified log-rank test (stratified on Rai stage, intermediate vs. high, and del(17p13.1) by FISH, present vs. absent). The Kaplan-Meier method will be used to estimate PFS distributions. Five-year PFS estimates, medians, and corresponding hazard ratios will be provided with 95% confidence intervals for each treatment strategy. Differences in five-year PFS estimates between the treatment strategies will be tested using a stratified chi-square test based on the complementary log-log transformation of the Kaplan-Meier estimates.

Best achieved response, up through the Cycle 15 Day 1 response assessment, will be determined. Response criteria are defined in Section 11.0 and for the purposes of recording best response will be categorized according to the following hierarchy: CR/CRi/CCR/nPR/PR/PRL/SD/PD. BM MRD negative will be defined as <1 CLL cell per

10,000 leukocytes in the bone marrow. BM MRD- CR rate will be calculated, and will be estimated using the number of patients meeting the BM MRD- CR criteria divided by the total number of patients randomized to each of the treatment arms (IO, IVO). Assuming that the incidence of BM MRD- CR is binomially distributed, we will calculate corresponding binomial 95% confidence intervals for the true rates. The stratified Cochran-Mantel-Haenszel test will be used to compare the BM MRD- CR rates between treatment arms (stratified on Rai stage, intermediate vs. high, and del(17p13.1) by FISH, present vs. absent). Similar analysis methods will be used to compare MRD- rates (BM and PB) between treatment arms. Specific to the comparison of MRD- rates, sensitivity analyses will be carried out conditional on the number of patients who submit a sample for MRD and with an informative MRD result, and by exploring the impact of missing data through techniques such as worst-case scenario or tipping-point analyses. In addition, the degree of response will be summarized with frequencies and percentages in two ways: first using physical exams with CT scans and second using physical exams only to categorize response. Lastly, PFS and OS landmarked at Cycle 16 Day 1 will be described by MRD response status and by treatment course using Cycle 15 Day 1 MRD and response assessments.

OS is defined from randomization date until death from any cause, censoring patients alive at the date of last contact. The Kaplan-Meier method will be used to estimate the OS distribution for each treatment strategy. Estimates at 5 years will be calculated with corresponding 95% confidence intervals, and differences in these estimates between the treatment strategies will be tested using a stratified chi-square test based on the complementary log-log transformation of the Kaplan-Meier estimates. Comparisons in OS curves between experimental and control treatment strategies will use a stratified log-rank test (stratified on Rai stage, intermediate vs. high, and del(17p13.1) by FISH, present vs. absent). Hazard ratios with 95% confidence intervals will be estimated from the corresponding, stratified proportional hazard model.

Toxicity and tolerability measures will be monitored regularly. Frequency and severity of adverse events and tolerability for each treatment strategy group will be summarized using descriptive statistics. As per NCI CTCAE v5.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described. We will also assess tolerability through assessing the number of patients who require dose modifications and/or dose delays, and the proportion of patients who go off treatment due to adverse events. Further, toxicity and tolerability measures will be assessed by treatment course. All patients who have received at least one dose of any of the therapeutic agents in a treatment regimen will be evaluable for toxicity and tolerability.

Proportional hazard models will be used in a multivariable analysis to identify baseline variables associated with PFS/OS and logistic regression models will be used in a multivariable analysis to identify baseline variables associated with response and/or specific toxicities of interest. Baseline variables will include but not be limited to presence of complex karyotype (>3 abnormalities), presence of TP53 mutations, and nodal size (> 10 cm).

13.5 Monitoring the study

13.5.1 Adverse event stopping rule

A safety monitoring rule will be applied to guide accrual suspension decisions based on unacceptable toxicity. The safety monitoring rule will be evaluated for all patients who begin treatment and during the time period prior to ibrutinib maintenance or observation. The safety rule will signal whether the proportion of patients who permanently discontinue therapy due to grade 3 or higher adverse events (including patients who died during active treatment) is significantly higher with IVO vs. IO. It is not anticipated that the percentage of patients who discontinue IO therapy due to grade 3 or higher adverse events will be more than 10-15%. The safety rule corresponds to a two-sample test of proportions with 85% power to detect an increase of 10 percentage points (i.e., 10% vs. 20%) with 454 patients, while constraining the overall one-sided type I error to 0.05. It uses a z-statistic based on the difference in two proportions and pooling the variance, with interim analyses planned after each successive group of approximately 45 patients are evaluated for the safety endpoint at roughly 1 year. To control the type I error rate across these comparisons, the Pocock version of the Lan-Demets error spending function was utilized. If this boundary is crossed, the data will be reviewed more closely and shared with the NCI as well as the Alliance DSMB so that consensus regarding temporary suspension of accrual, protocol modifications, or in the worst case scenario, decision to close the trial early may be made. The interim analysis and boundary characteristics were generated using the EAST version 6.4 software (Cytel Inc.) The boundary is shown below on the z-scale and on the effect scale (i.e., difference in proportions for the IVO versus IO treatment arms).

Information Fraction	Cumulative Sample Size	Approximate Analysis Time (Months)	Cumulative Alpha Spent	Boundary on the Z scale	Corresponding Boundary on the Treatment Effect Scale
0.10	45	18	0.008	2.412	0.260
0.20	91	21	0.015	2.363	0.180
0.30	136	25	0.021	2.317	0.144
0.40	182	29	0.026	2.280	0.123
0.50	227	33	0.031	2.250	0.108
0.60	272	37	0.035	2.225	0.098
0.70	318	40	0.039	2.204	0.090
0.80	363	44	0.043	2.187	0.083
0.90	409	48	0.047	2.171	0.078
1.00	454	52	0.050	2.158	0.073

13.5.2 Accrual monitoring stopping rule

Accrual will be monitored closely with monthly reports. Investigators will evaluate accrual after the first year of study activation. If accrual during this time period is less than 50% of what was projected to meet accrual goals, the study team will work together with the Data Monitoring Committee and the National Cancer Institute to plan for modifications, including the potential for closure.

13.5.3 Monitoring of non-protocol CLL therapy

Reasons for starting non-protocol CLL therapy in the absence of a documented progression will be described in study reports provided to the Alliance DSMB. In addition, the proportion of patients who start non-protocol CLL therapy in the absence of a documented progression will be summarized and compared between treatment arms. A Fisher's exact test will be used to identify if there is an imbalance in the proportions that may compromise the primary endpoint, and the study team will work together with the DSMB and the NCI to plan for possible modifications.

13.6 Study reporting

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patients-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website (https://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

13.7 Inclusion of women and minorities

It is the intent of the Alliance to enroll patients regardless of sex or race. Both men and women of all races and ethnic groups are eligible for this study. In the development of this protocol, the possibility of inherent sex or racial/ethnic differences in treatment response has been considered.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	0	0	2
Asian	1	3	0	0	4
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	7	13	0	0	20
White	117	240	7	13	377
More Than One Race	1	2	0	0	3
Total	128	260	7	13	408

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	14	30	0	0	42
More Than One Race	0	0	0	0	0

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Total	15	31	0	0	46

14.0 CORRELATIVE AND COMPANION STUDIES

There will be optional biobanking for future correlative science studies, and all patients are encouraged to participate.

14.1 Correlative Studies

14.1.1 Background

Previous CLL research identified specific markers including cytogenetic abnormalities, IgVH mutational status, and specific DNA mutations such as TP53 that predict both the natural history of this disease and response with specific therapies. With ibrutinib, studies performed in the relapsed setting have shown that some traditional prognostic factors such as del(17p13.1) and complex karyotype are important, while others such as del(11q22.3) and IGHV mutational status may not be. [22] [7] As well with venetoclax, data suggest that del(17p13.1) might be important, [8] but TP53 mutations may not be. [9] There are no data yet to determine whether these traditional markers will be important for patients undergoing combination therapy. Additionally, previous studies have predominantly been performed in patients with relapsed CLL, so the relevance to previously untreated disease is unclear.

As an important part of this trial, we will collect samples from each patient which will be banked for future studies. In addition to samples collected at baseline, we will obtain samples from each patient at Cycle 15 Day 1, every 6 cycles until cycle 84, and then every 12 cycles for up to 10 years, and time of progression. These samples will be saved in the Alliance Hematologic Malignancy Biorepository for future use. The banked specimens will not be used prior to specific approval by CTEP.

14.1.2 Sample Requirements

The sample requirements are outlined in Section 6.2.

14.1.3 Correlative Studies

Peripheral blood MRD determination by clonoSEQ (Adaptive biotechnologies) next generation sequencing (NGS). The clonoSEQ assay uses multiplex polymerase chain reaction (PCR) and NGS to identify and quantify rearranged IgH, IgK, and IgL sequences to identify and monitor specific disease clonotypes. MRD by NGS has been shown to be extremely sensitive with limit of detection of 1 CLL cell in 1,000,000 leukocytes (10-6). Whether this increased sensitivity is important for prognosis with venetoclax-based therapy is not known. Banked samples at baseline and C15D1 (peripheral blood) will be sent to Adaptive Biotechnologies for clonoSEQ NGS. Peripheral blood MRD status (positive vs negative) from C15D1 and measured by both standard central flow cytometry and clonoSEQ will be compared and reported using a common 2x2 frequency table. Sensitivity and specificity using flow cytometry results as the reference, as well as 1 minus specificity which is the measure of most interest, will be reported with 95% confidence intervals. To determine the added benefit of peripheral blood MRD determination by clonoSEQ, clinical outcomes will be analyzed in an exploratory manner. Descriptive statistics (percentages and 95% confidence intervals) will be calculated to estimate the number of patients who achieved CR among patients who are MRD negative by flow but MRD positive by NGS and patients who are MRD negative by flow and NGS in each treatment arm. We will

summarize the number of PFS events when they occur and will estimate Kaplan-Meier curves to illustrate PFS distributions.

15.0 REFERENCES

1. Byrd, J.C., et al., *Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib.* Blood, 2015. **125**(50616): p. 2497-506.
2. Burger, J.A., et al., *Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia.* N Engl J Med, 2015. **373**(25): p. 2425-37.
3. Woyach, J.A., et al., *Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib.* N Engl J Med, 2014. **370**(24): p. 2286-94.
4. O'Brien, S., et al., *Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study.* Lancet Oncol, 2016. **17**(10): p. 1409-1418.
5. Barr, P., et al., *Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia* Blood (ASH Annual Meeting Abstracts), 2016. **128**: p. Abstract 234.
6. Jaglowski, S.M., et al., *Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study.* Blood, 2015. **126**(7): p. 842-50.
7. O'Brien, S., et al., *Five-year experience with single agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.* Blood (ASH Annual Meeting Abstracts), 2016: p. Abstract 233.
8. Roberts, A.W., et al., *Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia.* N Engl J Med, 2016. **374**(4): p. 311-22.
9. Stilgenbauer, S., et al., *Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study.* Lancet Oncol, 2016. **17**(6): p. 768-78.
10. Seymour, J.F., et al., *Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia-results from a pre-planned interim analysis of the randomized phase 3 MURANO study.* Blood (ASH Annual Meeting Abstracts), 2017: p. Abstract LBA-2.
11. Seymour, J.F., et al., *Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study.* Lancet Oncol, 2017. **18**(2): p. 230-240.
12. Cervantes-Gomez, F., et al., *Pharmacological and Protein Profiling Suggests Venetoclax (ABT-199) as Optimal Partner with Ibrutinib in Chronic Lymphocytic Leukemia.* Clin Cancer Res, 2015. **21**(16): p. 3705-15.
13. Woodland, R.T., et al., *Regulation of B cell survival in xid mice by the proto-oncogene bcl-2.* J Immunol, 1996. **156**(6): p. 2143-54.
14. Rogers, K.A., et al., *Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia.* Blood, 2018. **132**(15): p. 1568-1572.
15. Goede, V., et al., *Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.* N Engl J Med, 2014. **370**(12): p. 1101-10.
16. Hallek, M., et al., *Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines.* Blood, 2008. **111**(12): p. 5446-56.
17. De Francesco, M.A., et al., *Different sequence strains of Streptococcus agalactiae elicit various levels of cytokine production.* Immunol Invest, 2008. **37**(8): p. 741-51.
18. Micallef, M.A. and M.L. Garg, *Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals.* Atherosclerosis, 2009. **204**(2): p. 476-82.
19. *This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.*

20. *Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.*
21. Cheson, B.D., et al., *National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment.* Blood, 1996. **87**(12): p. 4990-7.
22. Woyach, J.A., et al., *BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia.* J Clin Oncol, 2017. **35**(13): p. 1437-1443.

APPENDIX I CHILD-PUGH SCORE

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
Pugh RN, Murray-Lyon IM, Dawson L, et al . “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery, 1973;60: 646-9.

APPENDIX II HOWARD CRITERIA FOR TLS GRADING

Definitions of Laboratory and Clinical TLS*		
Metabolic Abnormality	**Criteria for Classification of Laboratory TLS**	**Criterial for Classification of Clinical TLS**
Hyperuricemia	Uric acid >8.0mg/dl	--
Hyperphosphatemia	Phosphorous >4.5 mg/dl	--
Hyperkalemia	Potassium >6.0 mmol/l	Cardiac dysrhythmia or sudden death probably of definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dl or ionized calcium <1.12**	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability, hypotension, or heart failure probably or definitely caused by hypocalcemia.
Acute kidney injury* **	--	Increase in the serum creatinine level of 0.3 mg/dl (26.5µmol/l)(or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5mg/kg/hr for 6 hours)

* In laboratory TLS, two or more metabolic abnormalities must be present during the same 24 hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death

** The corrected calcium level in mg/dl = measured calcium in mg/dl + 0.8 x (4-albumin in g/dl)

*** Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dl or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical TLS.

Taken from: Howard, SC, Jones DP, Pui C-H. “The tumor lysis syndrome.” NEJM 2011:364:1844-54.

APPENDIX III COLLABORATIVE AGREEMENT

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (https://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: https://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"0.

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborators to develop, obtain regulatory approval or commercialize its own Agent
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (https://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if application, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results for this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for the non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure the Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to ncicteppubs@mail.nih.gov. The Regulator Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript, or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

APPENDIX IV IBRUTINIB PATIENT MEDICATION DIARY

Version #02

Today's Date: _____ Agent: _____

Patient Name (initial acceptable): _____ Patient Study ID: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take your **ibrutinib**.
2. You will take **ibrutinib** on days 1-28.
3. Record the date, the number of capsules of each size you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross is out with one line, put your initials next to it, and then write the corrected information next to your initials. Examples: ~~10:30am~~ SB 9:30AM
5. Take ibrutinib with 8 ounces (approximately 240ml) of water. The capsules are to be swallowed intact. Take your dose about the same time each day. If a dose is missed, it should be taken as soon as possible within 8 hours of the missed dose on the same day with a return to the normal schedule the following day. Do not take extra capsules to make up the missed dose.
6. Please return this form to your physician when you go for your next appointment.

Cycle #: _____

Day	Date	Time of Dose	# of capsules	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				

17				
Day	**Date**	**Time of Dose**	**# of capsules**	**Comments**
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Physician's Office will complete this section:

1. Date patient started protocol treatment: _____
2. Date patient was removed from study: _____
3. Patient's dose cohort: _____
4. Total number of capsules taken this month (each size): _____
5. Physician/Nurse/Data Manager's Signature: _____

Patients Signature: _____

APÉNDICE IV DIARIO DE MEDICACIÓN DEL PACIENTE CON IBRUTINIB

Versión n.º 02

Fecha de hoy: _____ Agente: _____

Nombre del paciente (inicial aceptable): _____
Identificación del estudio del paciente: _____

INSTRUCCIONES PARA EL PACIENTE:

1. Complete un formulario por cada período de 4 semanas mientras toma su **ibrutinib**.
2. Tomará **ibrutinib** los días 1 a 28.
3. Registre la fecha, la cantidad de cápsulas de cada tamaño que tomó y cuándo las tomó. Registre las dosis tan pronto como las tome; no agrupe las entradas juntas en un momento posterior.
4. Si tiene algún comentario o nota algún efecto secundario, regístrelo en la columna Comentarios. Si comete un error al escribir, táchelo con una línea, coloque sus iniciales al lado y luego escriba la información corregida junto a sus iniciales. Ejemplos: ~~10:30 a.m.~~ SB 9:30 a.m.
5. Tome ibrutinib con 8 onzas (aproximadamente 240 ml) de agua. Las cápsulas deben tragarse intactas. Tome su dosis aproximadamente a la misma hora todos los días. Si se olvida una dosis, debe tomarse lo antes posible dentro de las 8 horas posteriores a la dosis olvidada el mismo día y volver al horario normal al día siguiente. No tome más cápsulas para alcanzar la dosis olvidada.
6. Entregue este formulario a su médico cuando vaya a su próxima cita.

Ciclo N.º: _____

Día	Fecha	Hora de la dosis	Cantidad de cápsulas	Comentarios
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				

16				
17				
Día	**Fecha**	**Hora de la dosis**	**Cantidad de cápsulas**	**Comentarios**
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

El consultorio del médico completará esta sección:

1. Date patient started protocol treatment: _____
2. Date patient was removed from study: _____
3. Patient's dose cohort: _____
4. Total number of capsules taken this month (each size): _____
5. Physician/Nurse/Data Manager's Signature:

Firma del paciente: _____

APPENDIX V VENETOCLAX PATIENT MEDICATION DIARY

Version #02

Today's Date: _____ Agent: _____

Patient Name (initial acceptable): _____ Patient Study ID: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take your **venetoclax**.
2. You will take **venetoclax** on days 1-28.
3. Record the date, the number of capsules of each size you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross is out with one line, put your initials next to it, and then write the corrected information next to your initials. Examples: ~~10:30am~~ SB 9:30AM
5. Take venetoclax with 8 ounces (approximately 240ml) of water. The capsules are to be swallowed intact. Take your dose about the same time each day. If a dose is missed, it should be taken as soon as possible within 8 hours of the missed dose on the same day with a return to the normal schedule the following day. Do not take extra capsules to make up the missed dose.
6. Please return this form to your physician when you go for your next appointment.

Cycle #: _____

Day	Date	Time of Dose	# of capsules	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				

17				
Day	**Date**	**Time of Dose**	**# of capsules**	**Comments**
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Physician's Office will complete this section:

1. Date patient started protocol treatment: _____
2. Date patient was removed from study: _____
3. Patient's dose cohort: _____
4. Total number of capsules taken this month (each size): _____
5. Physician/Nurse/Data Manager's Signature: _____

Patients Signature: _____

APÉNDICE V DIARIO DE MEDICACIÓN DEL PACIENTE DE VENETOCLAX

Versión n.º 02

Fecha de hoy: _____ Agente: _____

Nombre del paciente (inicial aceptable): _____
Identificación del estudio del paciente: _____

INSTRUCCIONES PARA EL PACIENTE:

1. Complete un formulario por cada período de 4 semanas mientras toma su **venetoclax**.
2. Tomará venetoclax los días 1 a 28.
3. Registre la fecha, la cantidad de cápsulas de cada tamaño que tomó y cuándo las tomó. Registre las dosis tan pronto como las tome; no agrupe las entradas juntas en un momento posterior.
4. Si tiene algún comentario o nota algún efecto secundario, regístrelo en la columna Comentarios. Si comete un error al escribir, táchelo con una línea, coloque sus iniciales al lado y luego escriba la información corregida junto a sus iniciales. Ejemplos: ~~10:30 a.m.~~ SB 9:30 a.m.
5. Tome venetoclax con 8 onzas (aproximadamente 240 ml) de agua. Las cápsulas deben tragarse intactas. Tome su dosis aproximadamente a la misma hora todos los días. Si se olvida una dosis, debe tomarse lo antes posible dentro de las 8 horas posteriores a la dosis olvidada el mismo día y volver al horario normal al día siguiente. No tome más cápsulas para alcanzar la dosis olvidada.
6. Entregue este formulario a su médico cuando vaya a su próxima cita.

Ciclo N.º: _____

Día	Fecha	Hora de la dosis	Cantidad de cápsulas	Comentarios
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				

16				
17				
Día	**Fecha**	**Hora de la dosis**	**Cantidad de cápsulas**	**Comentarios**
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

El consultorio del médico completará esta sección:

1. Date patient started protocol treatment: _____
2. Date patient was removed from study: _____
3. Patient's dose cohort: _____
4. Total number of capsules taken this month (each size): _____
5. Physician/Nurse/Data Manager's Signature:

Firma del paciente: _____

APPENDIX VI PATIENT DRUG INFORMATION HANDOUT AND WALLET CARDS

Version #03

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug combination of ibrutinib, venetoclax, and obinutuzumab. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Both ibrutinib and venetoclax interact with a certain specific enzyme in your liver. The enzyme(s) in question is/are CYP3A, where ibrutinib and venetoclax are primarily broken down by CYP3A enzymes, and therefore may be affected by other drugs that inhibit or induce this enzyme.

Venetoclax also may interact with certain transport proteins that help move drugs in and out of cells. The protein in question is P-gp and venetoclax may be moved in and out of cells by this protein.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Ibrutinib, venetoclax, and obinutuzumab may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Ibrutinib and venetoclax must be used very carefully with other medicines that use certain liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors or inducers of CYP3A.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid grapefruit products, Seville oranges, and starfruit during treatment
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug combination of ibrutinib, venetoclax, and obinutuzumab**.** This clinical trial is sponsored by the NCI. Ibrutinib and venetoclax may interact with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Ibrutinib and venetoclax interact with CYP3A, and must be used very carefully with other medicines that interact with this enzyme.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A.
- Before prescribing new medicines, your regular health care providers should check a frequently updated medical reference, such as with the FDA, for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APÉNDICE VI VOLANTE DE INFORMACIÓN SOBRE EL FÁRMACO PARA EL PACIENTE Y TARJETA PARA BILLETERA

Versión n.º 03

Información para los pacientes, sus cuidadores y el equipo de atención médica ajeno al estudio sobre posibles interacciones con otros fármacos y suplementos herbales

El paciente _____ está inscrito en un ensayo clínico que usa la combinación de fármacos experimentales en estudio ibrutinib, venetoclax y obinutuzumab. Este ensayo clínico está patrocinado por el Instituto Nacional del Cáncer. Este formulario está dirigido al paciente, pero incluye información importante para otras personas que atienden a este paciente.

Esto es lo que usted como proveedor de atención médica debe saber:

Tanto el ibrutinib como el venetoclax interactúan con una determinada enzima específica en su hígado. La enzima en cuestión es CYP3A, donde ibrutinib y venetoclax son degradados principalmente por las enzimas CYP3A y, por lo tanto, pueden verse afectados por otros fármacos que inhiben o inducen esta enzima.

Venetoclax también puede interactuar con ciertas proteínas de transporte que ayudan a que los fármacos entren y salgan de las células. La proteína en cuestión es P-gp y el venetoclax puede entrar y salir de las células mediante esta proteína.

Al paciente: Lleve este papel a sus citas médicas y guarde la tarjeta de información adjunta en su billetera.

Ibrutinib, venetoclax y obinutuzumab pueden interactuar con otros fármacos que pueden causar efectos secundarios. Por esta razón, es muy importante que informe a los médicos del estudio sobre cualquier medicamento que esté tomando antes de inscribirse en este ensayo clínico. También es muy importante que informe a sus médicos si deja de tomar algún medicamento habitual o si comienza a tomar un nuevo medicamento mientras participa en este estudio. Cuando hable con sus médicos sobre sus medicamentos actuales, incluya los medicamentos que compra sin receta (remedio de venta libre) o cualquier suplemento a base de hierbas como la hierba de San Juan. Es útil llevar con usted los envases de los medicamentos o una lista actualizada de los medicamentos.

Muchos proveedores de atención médica pueden hacer recetas de medicamentos. Debe informar a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras profesionales, farmacéuticos) que está participando en un ensayo clínico.

Esto es lo que usted y ellos deben saber:

Ibrutinib y venetoclax deben usarse con mucho cuidado con otros medicamentos que usan ciertas enzimas hepáticas. Antes de que usted se inscriba en el ensayo clínico, su médico del estudio trabajará con sus proveedores de atención médica habituales para revisar cualquier medicamento y suplemento herbal que se consideren inhibidores o inductores potentes de CYP3A.

- ¡Tenga mucho cuidado! Los medicamentos de venta libre (incluidos los suplementos herbales) pueden contener ingredientes que podrían interactuar con el fármaco del estudio. Hable con sus médicos o farmacéuticos para determinar si podría haber algún efecto secundario.

- Evite los productos de toronja, naranjas de Sevilla y carambola durante el tratamiento.
- Su proveedor de atención médica habitual debe consultar una fuente de consulta médica actualizada con frecuencia o llamar al médico del estudio antes de recetar cualquier medicamento nuevo o de suspender algún medicamento que esté tomando. El nombre de su médico del estudio es _____ y se lo/la puede contactar en _____.

TARJETA PARA LA BILLETERA CON INFORMACIÓN SOBRE EL FÁRMACO DEL ESTUDIO

Usted está inscrito en un ensayo clínico que usa la combinación de fármacos experimentales en estudio ibrutinib, venetoclax y obinutuzumab. Este ensayo clínico está patrocinado por el NCI. Ibrutinib y venetoclax pueden interactuar con fármacos que son procesados por su hígado. Por eso, es muy importante que:

- Informe a sus médicos si deja de tomar algún medicamento o si comienza a tomar algún medicamento nuevo.
- Informe a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras profesionales o farmacéuticos) que está participando en un ensayo clínico.
- Consulte con su médico o farmacéutico siempre que necesite usar un medicamento de venta libre o un suplemento herbal.

Ibrutinib y venetoclax interactúan con CYP3A y deben usarse con mucho cuidado con otros medicamentos que interactúan con esta enzima.

- Antes de que usted se inscriba en el ensayo clínico, su médico del estudio trabajará con sus proveedores de atención médica habituales para revisar cualquier medicamento y suplemento herbal que se consideren inductores/inhibidores potentes de CYP3A.
- Antes de recetar nuevos medicamentos, sus proveedores de atención médica habituales deben consultar una referencia médica actualizada con frecuencia, como la de la FDA, para obtener una lista de medicamentos que deben evitarse, o comunicarse con su médico del estudio.
- El nombre de su médico del estudio es

  _____ y se lo puede contactar

  en_____.